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## (54) Spiro piperidines and homologs which promote release of growth hormone

Spiropiperidine and ihre Homologen, die die Ausschüttung von Wachstumshormonen stimulieren

Spiro piperidines et ses homologues favorisants la libération de l'hormone de croissance

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(73) Proprietor: **Merck & Co., Inc.**
**Rahway New Jersey 07065-0900 (US)**

(72) Inventors:
- **Chen, Meng-Hsin**
  **Westfield, NJ 07090 (US)**
- **Patchett, Arthur A.**
  **Westfield, NJ 07090 (US)**
- **Johnston, David B.R.**
  **Warren, NJ 07060 (US)**
- **Tata, James R.**
  **Westfield, NJ 07090 (US)**
- **Nargund, Ravi P.**
  **East Brunswick, NJ 08816 (US)**
- **Yang, Lihu**
  **Edison, NJ 08820 (US)**

(74) Representative: **Thompson, John Dr. et al**
**Merck & Co., Inc.**
**European Patent Department**
**Terlings Park**
**Eastwick Road**
**Harlow, Essex CM20 2QR (GB)**

(56) References cited:
**EP-A- 0 144 230** **EP-A- 0 513 974**

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The file contains technical information submitted after the application was filed and not included in this specification



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## Description

### BACKGROUND OF THE INVENTION

**[0001]** Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic processes of the body:

1. Increased rate of protein synthesis in all cells of the body;
2. Decreased rate of carbohydrate utilization in cells of the body;
3. Increased mobilization of free fatty acids and use of fatty acids for energy.

**[0002]** A deficiency in growth hormone secretion can result in various medical disorders, such as dwarfism.

**[0003]** Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

**[0004]** In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering GRF or a peptidal compound which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone. Recently, recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray.

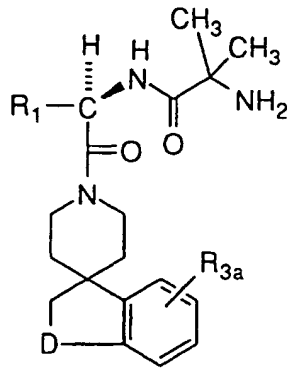
**[0005]** Other compounds have been developed which stimulate the release of endogenous growth hormone such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent 4,411,890. These peptides, while considerably smaller than growth hormones are still susceptible to various proteases. As with most peptides, their potential for oral bioavailability is low. The instant compounds are non-peptide analogs for promoting the release of growth hormone which are stable in a variety of physiological environments and which may be administered parenterally, nasally or by the oral route.

### SUMMARY OF THE INVENTION

**[0006]** The instant invention covers certain spiro compounds which have the ability to stimulate the release of natural or endogenous growth hormone. The compounds thus have the ability to be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food production where the stimulation of growth hormone will result in a larger, more productive animal. Thus, it is an object of the instant invention to describe the spiro compounds. It is a further object of this invention to describe procedures for the preparation of such compounds. A still further object is to describe the use of such compounds to increase the secretion of growth hormone in humans and animals. A still further object of this invention is to describe compositions containing the spiro compounds for the use of treating humans and animals so as to increase the level of growth hormone secretions. Further objects will become apparent from a reading of the following description.

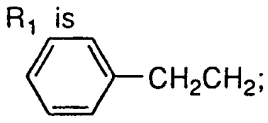
### DESCRIPTION OF THE INVENTION

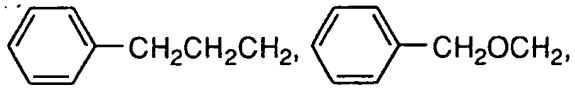
**[0007]** The novel spiro compounds of the instant invention are best described in the following structural formula V:

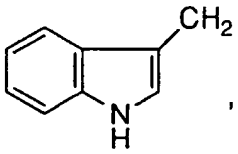


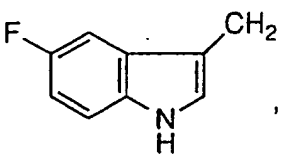
V

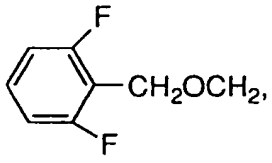
$R_1$ is

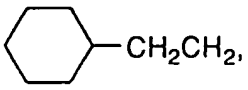


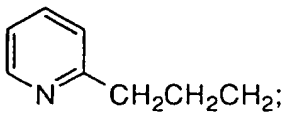


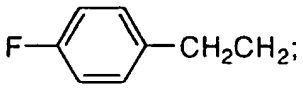


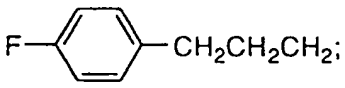






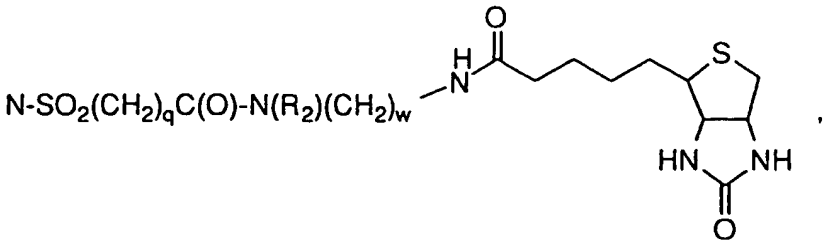


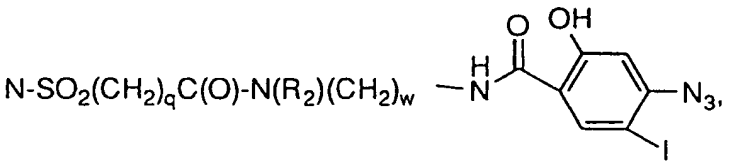


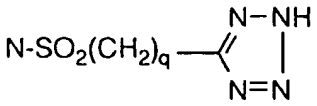


$R_{3a}$ is H, fluoro;

D is O, S, $S(O)_m$, $N(R_2)$, $NSO_2(R_2)$, $NSO_2(CH_2)_t$aryl, $NC(O)(R_2)$, $NSO_2(CH_2)_qOH$, $NSO_2(CH_2)_qCOOR_2$, $N\text{-}SO_2(CH_2)_qC(O)\text{-}N(R_2)(R_2)$, $N\text{-}SO_2(CH_2)_qC(O)\text{-}N(R_2)(CH_2)_wOH$,







and the aryl is phenyl or pyridyl and the phenyl may be substituted by 1-2 halogen;
$R_2$ is H, $C_1$-$C_4$ alkyl;
m = 1, 2;
t is 0, 1, 2;
q is 1, 2, 3;
w is 2-6;
and the pharmaceutically acceptable salts and individual diastereomers thereof.

**[0008]** In the above structural formula and throughout the instant specification, the following terms have the indicated meanings:

**[0009]** The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkyl groups are methyl, ethyl, propyl, ethinyl, isopropyl, butyl, sec-butyl, tertiary butyl, allyl, propenyl, butenyl, butadienyl and the like.

**[0010]** The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

**[0011]** Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other.

**[0012]** Representative most preferred growth hormone releasing compounds of the present invention include the following:

1. N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide

2. N-[1(R)-[(1,2-Dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide

3. N-[1(R)-[(1,2-Dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide

6. N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethyloxy) ethyl]-2-amino-2-methylpropanamide

7. N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethyloxy)

ethyl]-2-amino-2-methylpropanamide mesylate salt

8. N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide

9.N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide

11. N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-3-phenylpropyl]-2-amino-2-methylpropanamide

12. N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methylpropanamide

13. N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-4-phenylbutyl]-2-amino-2-methylpropanamide

14. N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide

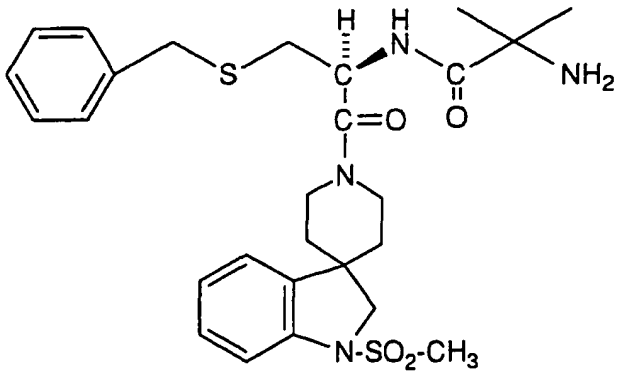
15. N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide

16. N-[1(R)-[(1,2-Dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl] -2-(1H-indol-3-yl)ethyl] -2-amino-2-methylpropanamide

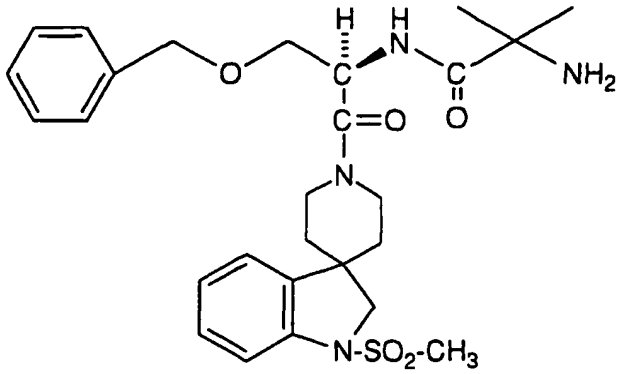
17. N-[1(R)-[(1,2-Dihydro-1,1dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl] -2-(phenylmethyloxy) ethyl] -2-amino-2-methylpropanamide

and pharmaceutically acceptable salts thereof.

**[0013]** Representative examples of the nomenclature employed are given below:




\N-[1(S)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl] -2-(phenylmethylthio)ethyl] -2-amino-2-methylpropanamide



N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide

**[0014]** Throughout the instant application, the following abbreviations are used with the following meanings:

| | |
|---|---|
| BOC | t-butyloxycarbonyl |
| BOP | Benzotriazol-1-yloxy tris/dimethylamino)phosphonium hexafluorophosphate |
| CBZ | Benzyloxycarbonyl |
| DCC | Dicyclohexylcarbodiimide |
| DMF | N,N-dimethylformamide |
| EDC | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride |
| FAB-MS | Fast atom bombardment-mass spectroscopy |
| GHRP | Growth hormone releasing peptide |
| HOBT | Hydroxybenztriazole |
| LAH | Lithium aluminum hydride |
| HPLC | High pressure liquid chromatography |
| MHz | Megahertz |
| MPLC | Medium pressure liquid chromatography |
| NMM | N-Methylmorpholine |
| NMR | Nuclear Magnetic Resonance |
| OXONE | Potassium peroxy monosulfate |
| PLC | Preparative layer chromatography |
| PCC | Pyridinium chlorochromate |
| Ser | Serine |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofuran |
| TLC | Thin layer chromatography |
| TMS | Tetramethylsilane |

**[0015]** The compounds of the instant invention all have at least one asymmetric centre as noted in the structural formula V above.

**[0016]** Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers, racemic mixtures or diastereomeric mixtures thereof, be included within the ambit of the instant invention.

**[0017]** The instant compounds are generally isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic, methane sulfonic and the like. In addition, certain compounds containing an acidic function such as a carboxy can be isolated in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

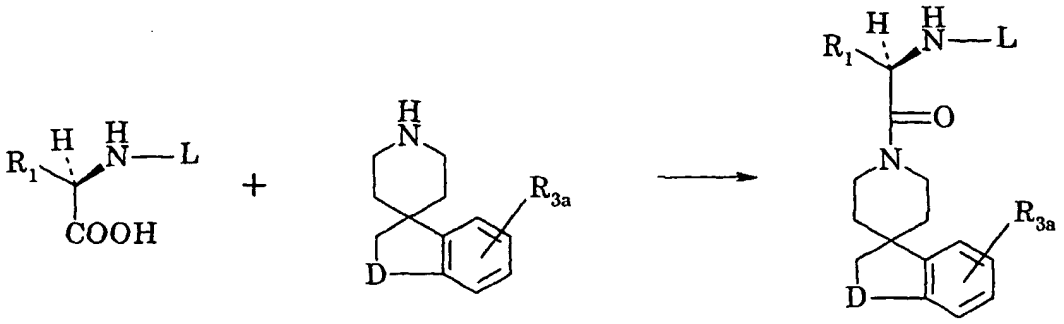
**[0018]** The preparation of compounds of the present invention can be carried out in sequential or convergent synthetic

routes. Syntheses detailing the preparation of the compounds of Formula V in a sequential manner are presented in the following reaction schemes.

**[0019]** The protected amino acid derivatives **1** are, in many cases, commercially available where the protecting group L is, for example, BOC or CBZ groups. Other protected amino acid derivatives **1** can be prepared by literature methods. Many of the spiro piperidines of formula 2 are known in the literature and can be derivatized on the phenyl or heteroaryl by standard means, such as halogenation, nitration, sulfonylation, etc. Alternatively, various phenyl or heteroaryl substituted spiro piperidines can be prepared following literature methods using derivatized phenyl and heteroaryl intermediates.

**[0020]** Intermediates of formula **3** can be synthesized as described in Scheme 1. Coupling of spiro piperidines of formula **2** to protected amino acids of formula **1**, wherein L is a suitable protecting group, is conveniently carried out in an inert solvent such as dichloromethane by a coupling reagent such as DCC or EDC in the presence of HOBT. Alternatively, the coupling can also be effected with a coupling reagent such as BOP in an inert solvent such as dichloromethane. Separation of unwanted side products, and purification of intermediates is achieved by chromatography on silica gel, employing flash chromatography (W. C. Still, M. Kahn, and A. Mitra *J. Org. Chem.* **1978**, *43*, 2923), MPLC or preparative TLC.

SCHEME 1




1 2 3

**[0021]** Conversion of **3** to intermediates **4** can be carried out as illustrated in Scheme 2. Removal of benzyloxycarbonyl groups can be achieved by a number of methods known in the art; for example, catalytic hydrogenation with hydrogen in the presence of palladium or platinum catalyst in a protic solvent such as methanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, removal of benzyloxy carbonyl groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid. Removal of BOC protecting groups is carried out in a solvent such as methylene chloride or methanol, with a strong acid, such as hydrochloric acid or trifluoroacetic acid. Conditions required to remove other protecting groups which may be present can be found in Greene, T; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, NY 1991.

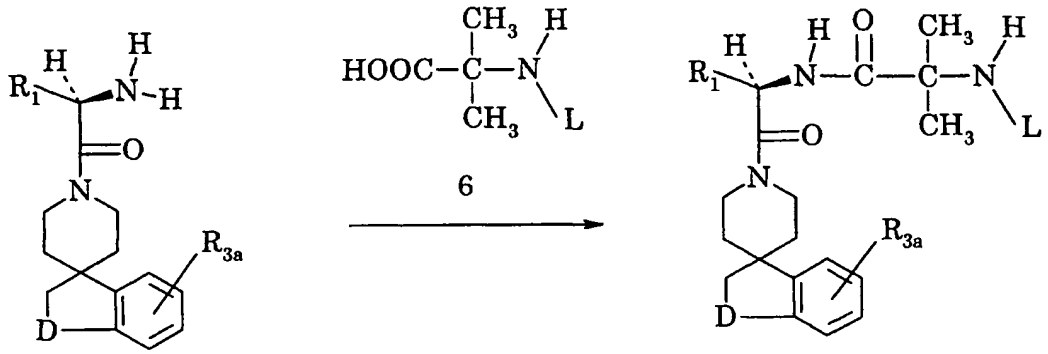
SCHEME 2


3 4

**[0022]** Intermediates of formula **5** can be prepared as shown in Scheme 3 by coupling of intermediates of formula **4** to amino acids of formula **6**, once again, in an inert solvent such as dichloromethane by a coupling reagent such as EDC or DCC in the presence of HOBT. These amino acids 6 are known amino acids or amino acids readily synthesized by methods known to those skilled in the art. Alternatively, the coupling can also be effected with a coupling reagent such as BOP in an inert solvent such as dichloromethane.

**[0023]** Deprotection of **5** (L = protecting group) can be carried out under conditions known in the art.

SCHEME 3



4 6 5

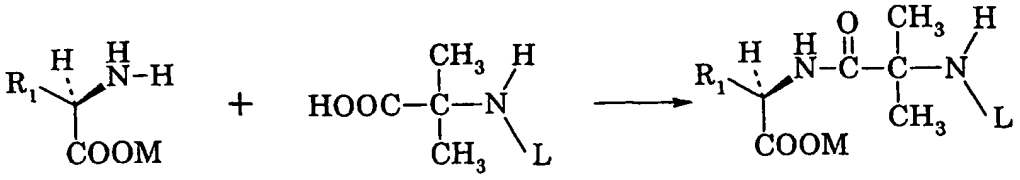
**[0024]** The compounds of the present invention can also be prepared in a convergent manner as described in reaction schemes 6, 7 and 8.

**[0025]** The protected amino acid derivatives **10** are, in many cases, commercially available where M = methyl, ethyl, or benzyl esters. Other ester protected amino acids can be prepared by classical methods familiar to those skilled in the art. Some of these methods include the reaction of a protected amino acid with a diazoalkane and removal of a protecting group L, the reaction of an amino acid with an appropriate alcohol in the presence a strong acid like hydrochloric acid or p-toluenesulfonic acid. Synthetic routes for the preparation of new amino acids are described in Schemes

14, 15, and 16.

**[0026]** Intermediates of formula **11** can be prepared as shown in Scheme 6 by coupling of amines **10** to amino acids **6** wherein L is a protecting group, as described above in Scheme 3.

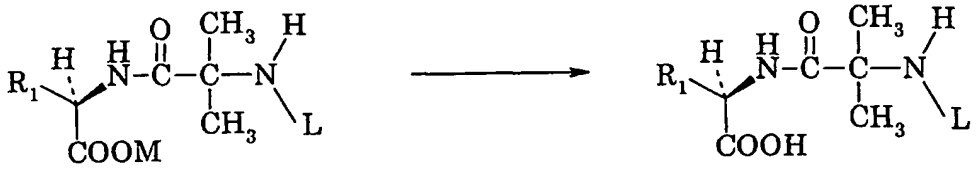
SCHEME 6



10 6 11

**[0027]** Conversion of the ester **11** to intermediate acids **12** can be achieved by a number of methods known in the art as described in Scheme 7; for example, methyl and ethyl esters can be hydrolyzed with lithium hydroxide in a protic solvent like aqueous methanol. In addition, removal of benzyl group can be accomplished by a number of reductive methods including hydrogenation in the presence of platinum or palladium catalyst in a protic solvent such as methanol. An allyl ester can be cleaved with tetrakis-triphenylphosphine palladium catalyst in the presence of 2-ethylhexanoic acid in a variety of solvents including ethyl acetate and dichloromethane (see *J. Org. Chem.* **1982**, *42*, 587).

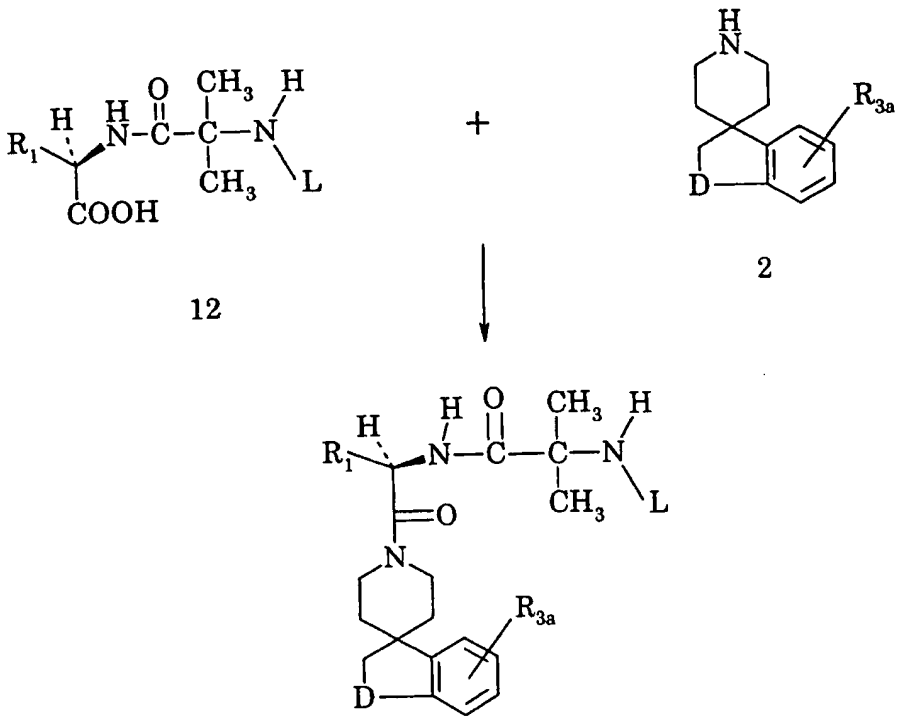
SCHEME 7



11 12

**[0028]** Acid **12** can then be elaborated to **5** as described in Scheme 8. Coupling of spiro piperidines of formula **2** to acids of formula **12** wherein L is a suitable protecting group, is conveniently carried out in an inert solvent such as dichloromethane by a coupling reagent such as dicylohexyl carbodiimide (DCC) or EDC in the presence of 1-hydroxy-benztriazole (HOBT). Alternatively, the coupling can also be effected with a coupling reagent such as benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate ("BOP") in an inert solvent such as dichloromethane. Transformation of **5** to V is achieved by removal of the protecting group L.

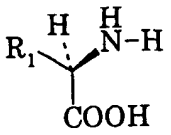
SCHEME 8



12 2 5

[0029] The compounds of the present invention are prepared from a variety of substituted natural and unnatural amino acids such as those of formulas **30.** The preparation of many of these acids has been described in the US patent 5206237.

[0030] The preparation of these intermediates in racemic form is accomplished by classical methods familiar to those skilled in the art (Williams, R. M. *"Synthesis of Optically Active α-Amino Acids"* Pergamon Press: Oxford, 1989; Vol. 7). Several methods exist to resolve (DL)-



30

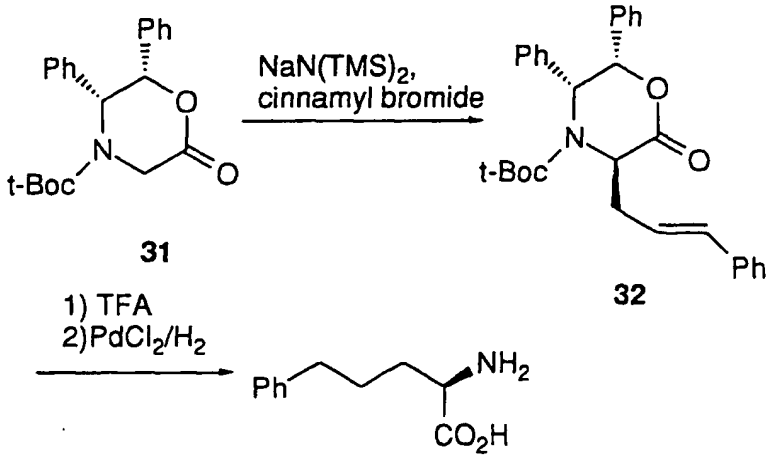
amino acids. One of the common methods is to resolve amino or carboxyl protected intermediates by crystallization of salts derived from optically active acids or amines. Alternatively, the amino group of carboxyl protected intermediates can be coupled to optically active acids by using chemistry described earlier. Separation of the individual diastereomers either by chromatographic techniques or by crystallization followed by hydrolysis of the chiral amide furnishes resolved amino acids. Similarly, amino protected intermediates can be converted to a mixture of chiral diastereomeric esters and amides. Separation of the mixture using methods described above and hydrolysis of the individual diastereomers

provides (D) and (L) amino acids. Finally, an enzymatic method to resolve N-acetyl derivatives of (DL)-amino acids has been reported by Whitesides and coworkers in *J. Am. Chem. Soc.* **1989,** *111,* 6354-6364.

**[0031]** When it is desirable to synthesize these intermediates in optically pure form, some established methods include: (1) asymmetric electrophilic amination of chiral enolates (*J. Am. Chem. Soc.* **1986,** *108,* 6394-6395, 6395-6397, and 6397-6399), (2) asymmetric nucleophilic amination of optically active carbonyl derivatives, (*J. Am. Chem. Soc.* **1992,** *114,* 1906; *Tetrahedron Lett.* **1987,** *28,* 32), (3) diastereoselective alkylation of chiral glycine enolate synthons (*J. Am. Chem. Soc.* **1991,** *113,* 9276; *J. Org. Chem.* **1989,** *54,* 3916), (4) diastereoselective nucleophilic addition to a chiral electrophilic glycinate synthon (*J. Am. Chem. Soc.* **1986,** *108,* 1103), (5) asymmetric hydrogenation of prochiral dehydroamino acid derivatives (*"Asymmetric Synthesis, Chiral Catalysis*; Morrison, J. D., Ed; Academic Press: Orlando, FL, 1985; Vol 5), and (6) enzymatic syntheses (*Angew. Chem. Int. Ed. Engl.* **1978,** *17,* 176).

**[0032]** For example, alkylation of the enolate of diphenyloxazinone **31** (*J. Am. Chem. Soc.* **1991,** *113,* 9276) with cinnamyl bromide in the presence of sodium bis(trimethylsilyl)amide proceeds smoothly to afford **32** which is converted into the desired (D)-2-amino-5-phenylpentanoic acid **33** by removing the N-t-butyloxycarbonyl group with trifluoroacetic acid and hydrogenation over a $PdCl_2$ catalyst (Scheme 14)

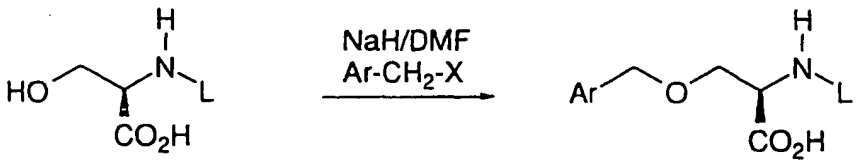
SCHEME 14




**31** **32** **33**

**[0033]** Intermediates of formula **30** which are O-benzyl-(D)-serine derivatives **34** are conveniently prepared from suitably substituted benzyl halides and N-protected-(D)-serine **34**. The protecting group L is conveniently a BOC or a CBZ group. Benzylation of **34** can be achieved by a number of methods well known in the literature including deprotonation with two equivalents of sodium hydride in an inert solvent such as DMF followed by treatment with one equivalent of a variety of benzyl halides (*Synthesis* **1989,** 36) as shown in Scheme 15.

SCHEME 15



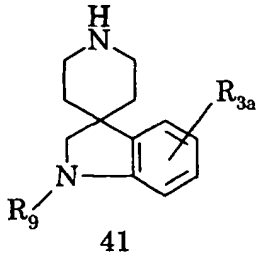

**34** **35**

**[0034]** The O-alkyl-(D)-serine derivatives are also prepared using the alkylation protocol shown in Scheme 15. Other

methods that could be utilized to prepare (D)-serine derivatives of formula **35** include the acid catalyzed benzylation of carboxyl protected intermediates derived from **34** with reagents of formula $ArCH_2OC(=NH)CCl_3$ (O. Yonemitsu et al. *Chem. Pharm. Bull.* **1988,** *36,* 4244). Alternatively, alkylation of the chiral gylcine enolates (*J. Am. Chem. Soc.* **1991,** *113,* 9276; *J. Org. Chem.* **1989,** *54,* 3916) with $ArCH_2OCH_2X$ where X is a leaving group affords 35. In addition D,L-O-aryl(alkyl)serines can be prepared and resolved by methods described above.

**[0035]** Hence, a variety of substituted amino acids may be incorporated into a growth hormone secretagogue via the chemistry detailed in Schemes 1 and 8. Removal of amino protecting groups can be achieved by a number of methods known in the art; as described above and in Protective Groups in Organic Synthesis T.W. Greene, John Wiley and Sons, NY. 1981.

**[0036]** The spiro piperidines of formula **41** can be prepared by a number of methods, including the syntheses as described below.



41

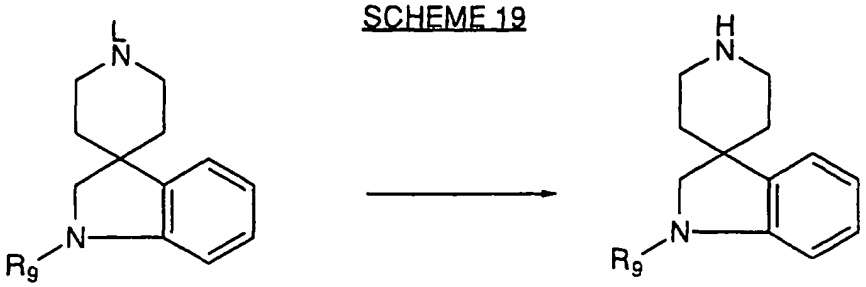
**[0037]** The spiropiperidines of formula **42**, wherein L is a defined protecting group, can be synthesized by methods that are known in the literature (for example H. Ong et al *J. Med. Chem.* **1983,** *23,* 981-986). The indoline nitrogen of **42,** wherein L is a protecting group such as methyl or benzyl, can be reacted by with a variety of electrophiles to yield spiro piperidines of formula **43,** wherein $R_9$ can be a variety of functionalities. Compound **42** can be reacted with, for example, isocyanates in an inert solvent like dichloromethane to yield urea derivatives, chloroformates in an inert solvent like dichloromethane to yield carbamates, acid chlorides,

SCHEME 18

42 43

anhydrides, or acyl imidazoles to generate amides, sulfonyl chlorides to generate sulfonamides, sulfamyl chlorides to yield sulfamides. Also, the indoline nitrogen of **42** can be reductively alkylated with aldehydes with conditions known in the art. When the aldehyde used in the reductive amination reaction is a protected glyoxylic acid of structure HCO-COOM, wherein M is a defined protecting group, M can be removed from the product and further derivatized. Alternatively, **42** can be reacted with epoxides to produce **43,** wherein $R_9$ is β-hydroxy-substituted alkyl or arylalkyl groups. The indoline **42** can also be transformed to compounds of formula **43,** wherein $R_9$ = phenyl or substituted phenyl, heteroaryl or substituted heteroaryl, by carrying out the reacting **42** with a fluoro phenyl or fluoro heteroaryl reagent. This chemistry is detailed in H. Ong et al *J. Med. Chem.* **1983,** *23,* 981-986.

SCHEME 19

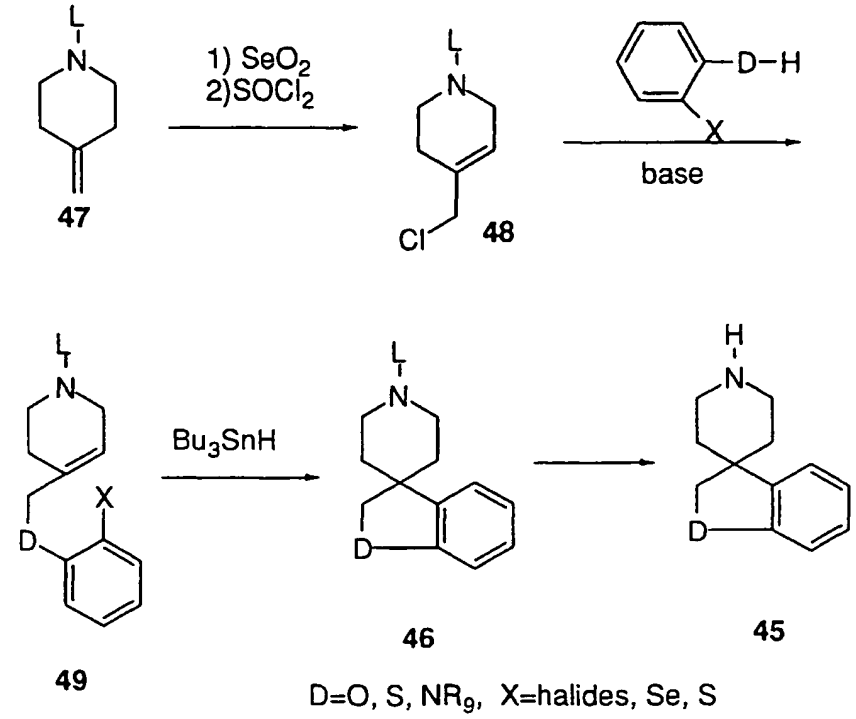


43 44

**[0038]** The spiro piperidine intermediate **43** (L = Me or Bn), wherein $R_9$ is hydrogen or most of the derivatives described above, can be demethylated or debenzylated to produce **44**, wherein $R_9$ is hydrogen or most of the derivatives described above, as shown in Scheme 19. For compounds of formula **43**, wherein L = Me, demethylation can be carried out by a number methods familiar those skilled in the art. For example, demethylation of **43** be accomplished by reacting it with cyanogen bromide and potassium carbonate in an inert solvent solvent such as dichloromethane to yield a cyanamide which can reduced to give **44** by treatment with lithium aluminum hydride in refluxing tetrahydrofuran, refluxing strong acid like aqueous hydrochloric acid, or with Grignard reagents like methyl magnesium bromide. Alternatively, demethylation of **43** can be effected with the ACE-Cl method as described in R. Olofson et al. *J. Org. Chem.* **1984**, *49*, 2795 and references therein. For intermediates of formula **43**, wherein L = Bn, removal of benzyl group can be accomplished by reductive methods including hydrogenation in the presence of platinum or palladium catalyst in a protic solvent like methanol. Alternatively, debenzylation of **43**, L = Bn, can be effected with the ACE-Cl method as described in R. Olofson et al. *J. Org. Chem.* **1984**

**[0039]** The spiro heterocyclic compounds **45** can be prepared by a number of methods, including the syntheses as described in Scheme 20.

SCHEME 20

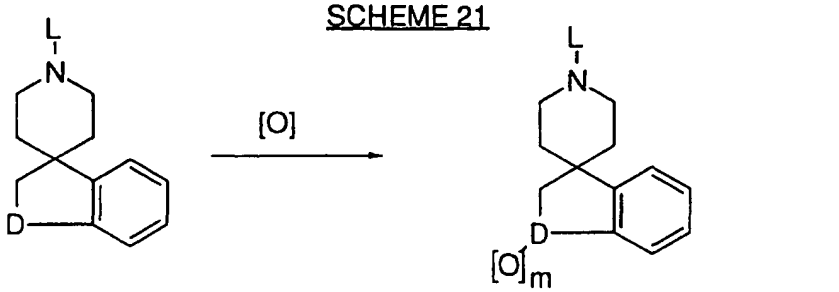



47 48 49 46 45

D=O, S, $NR_9$, X=halides, Se, S

Allylic oxidation of the protected piperidine **47** is accomplished by classical methods familiar to those skilled in the art (Rabjohn, N. *Org. React.* **1976**, *24*, 261). The resulting allylic alcohol is treated with thionyl chloride in an inert solvent such as benzene to provide the corresponding chloride **48**. When D=O or S, the alkylation is carried out in DMF or acetone as solvent with potassium carbonate as a base, and when D=$NR_9$ ($R_9$=H, alkyl, aryl, acyl, sulfonyl, carbamate) the reaction is carried out with sodium hydride as a base in an inert solvent such as THF to afford the cyclization precursor **49**. When L is a defined protecting group, compound **49** can be cyclized by a number methods familiar to those skilled in the art. For example, cyclization of **49** can be accomplished by reaction with tributyltin hydride (Curran, D. P. *Synthesis* **1988**, 417 and 489) in an inert solvent such as benzene to yield **46**. Alternatively, compound **46** (D=$NR_9$) can be prepared by the method shown in Schemes 18 and 19. When D=S, compound **46** can be oxidised to the sulfoxide **46** (m=1) and the sulfone **46** (m=2) by many oxidizing agents (Scheme 21). For example, sodium periodate is often used for the synthesis of sulfoxides and OXONE is used for the synthesis of sulfones. Removal of the protecting group provides the amine **45** which then can be incorporated into a growth hormone secretagogue via the chemistry detaileds in Scheme 1 and 8 shown above which utilize generic intermediate **2**.

SCHEME 21




46 D=S

46 D = $S(O)_m$ m=1,2

**[0040]** It is noted that the order of carrying out the foregoing reaction schemes is not significant and it is within the skill of one skilled in the art to vary the order of reactions to facilitate the reaction or to avoid unwanted reaction products.

**[0041]** The growth hormone releasing compounds of Formula V are useful *in vitro* as unique tools for understanding how growth hormone secretion is regulated at the pituitary level. This includes use in the evaluation of many factors thought or known to influence growth hormone secretion such as age, sex, nutritional factors, glucose, amino acids, fatty acids, as well as fasting and non-fasting states. In addition, the compounds of this invention can be used in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that somatostatin inhibits growth hormone release. Other hormones that are important and in need of study as to their effect on growth hormone release include the gonadal hormones, e.g., testosterone, estradiol, and progesterone; the adrenal hormones, e.g., cortisol and other corticoids, epinephrine and norepinephrine; the pancreatic and gastrointestinal hormones, e.g., insulin, glucagon, gastrin, secretin; the vasoactive peptides, e.g., bombesin, the neurokinins; and the thyroid hormones, e.g., thvroxine and triiodothyronine. The compounds of Formula V can also be employed to investigate the possible negative or positive feedback effects of some of the pituitary hormones, e.g., growth hormone and endorphin peptides, on the pituitary to modify growth hormone release. Of particular scientific importance is the use of these compounds to elucidate the subcellular mechanisms mediating the release of growth hormone.

**[0042]** The compounds of Formula V can be administered to animals, including man, to release growth hormone *in vivo*. For example, the compounds can be administered to commercially important animals such as swine, cattle, sheep and the like to accelerate and increase their rate and extent of growth, to improve feed efficiency and to increase milk production in such animals. In addition, these compounds can be administered to humans *in vivo* as a diagnostic tool to directly determine whether the pituitary is capable of releasing growth hormone. For example, the compounds of Formula V can be administered *in vivo* to children. Serum samples taken before and after such administration can be assayed for growth hormone. Comparison of the amounts of growth hormone in each of these samples would be a means for directly determining the ability of the patient's pituitary to release growth hormone.

**[0043]** Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula V in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise an anabolic agent in addition to at least one of the compounds of Formula V or another composition which exhibits a different activity, e.g., an antibiotic growth permittant or an agent to treat osteoporosis or in combination with a corticosteroid to minimize the catabolic

side effects or with other pharmaceutically active materials wherein the combination enhances efficacy and minimizes side effects.

**[0044]** Growth promoting and anabolic agents include, but are not limited to, TRH, diethylstilbesterol, estrogens, β-agonists, theophylline, anabolic steroids, enkephalins, E series prostaglandins, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Patent No. 4,411,890.

**[0045]** A still further use of the growth hormone secretagogues of this invention is in combination with other growth hormone secretagogues such as the growth hormone releasing peptides GHRP-6, GHRP-1 as described in U.S. Patent Nos. 4,411,890 and publications WO 89/07110, WO 89/07111 and B-HT920 as well as hexarelin and the newly discovered GHRP-2 as described in WO 93/04081 or growth hormone releasing hormone (GHRH, also designated GRF) and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2 or α- adrenergic aginists such as clonidine or serotonin 5HTID agonists such as sumitriptan or agents which inhibit somatostatin or its release such as physostigmine and pyridostigmine.

**[0046]** As is well known to those skilled in the art, the known and potential uses of growth hormone are varied and multitudinous. Thus, the administration of the compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself. These varied uses of growth hormone may be summarized as follows: stimulating growth hormone release in elderly humans; treating growth hormone deficient adults; prevention of catabolic side effects of glucocorticoids, treatment of osteoporosis, stimulation of the immune system, acceleration of wound healing, accelerating bone fracture repair, treatment of growth retardation, treating acute or chronic renal failure or insufficiency, treatment of physiological short stature, including growth hormone deficient children, treating short stature associated with chronic illness, treatment of obesity and growth retardation associated with obesity, treating growth retardation associated with Prader-Willi syndrome and Turner's syndrome; accelerating the recovery and reducing hospitalization of burn patients or following major surgery such as gastrointestinal surgery; treatment of intrauterine growth retardation, skeletal dysplasia, hypercortisonism and Cushings syndrome; replacement of growth hormone in stressed patients; treatment of osteochondrodysplasias, Noonans syndrome, sleep disorders, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treatment of pulmonary dysfunction and ventilator dependency; attenuation of protein catabolic response after a major operation; treating malabsorption syndromes, reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; accelerating weight gain and protein accretion in patients on TPN (total parenteral nutrition); treatment of hyperinsulinemia including nesidioblastosis; adjuvant treatment for ovulation induction and to prevent and treat gastric and duodenal ulcers; to stimulate thymic development and prevent the age-related decline of thymic function; adjunctive therapy for patients on chronic hemodialysis; treatment of immunosuppressed patients and to enhance antibody response following vaccination; improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; stimulation of osteoblasts, bone remodelling, and cartilage growth; treatment of neurological diseases such as peripheral and drug induced neuropathy, Guillian-Barre Syndrome, amyotrophic lateral sclerosis, multiple sclerosis, cerebrovascular accidents and demyelinating diseases; stimulation of the immune system in companion animals and treatment of disorders of aging in companion animals; growth promotant in livestock; and stimulation of wool growth in sheep.

**[0047]** It will be known to those skilled in the art that there are numerous compounds now being used in an effort to treat the diseases or therapeutic indications enumerated above. Combinations of these therapeutic agents some of which have also been mentioned above with the growth hormone secretagogues of this invention will bring additional, complementary, and often synergistic properties to enhance the growth promotant, anabolic and desirable properties of these various therapeutic agents. In these combinations, the therapeutic agents and the growth hormone secretagogues of this invention may be independently present in dose ranges from one one-hundredth to one times the dose levels which are effective when these compounds and secretagogues are used singly.

**[0048]** Combined therapy to inhibit bone resorption, prevent osteoporosis and enhance the healing of bone fractures can be illustrated by combinations of bisphosphonates and the growth hormone secretagogues of this invention. The use of bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N.A.T., Role of Bisphosphonates in Metabolic Bone Diseases. *Trends in Endocrinol. Metab.*, 1993, *4*, 19-25. Bisphosphonates with these utilities include alendronate, tiludronate, dimethyl - APD, risedronate, etidronate, YM-175, clodronate, pamidronate, and BM-210995. According to their potency, oral daily dosage levels of the bisphosphonate of between 0.1 mg and 5 g and daily dosage levels of the growth hormone secretagogues of this invention of between 0.01 mg/kg to 20 mg/kg of body weight are administered to patients to obtain effective treatment of osteoporosis.

**[0049]** The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated in dosage forms appropriate for each route of administration.

**[0050]** Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as

sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

**[0051]** Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

**[0052]** Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

**[0053]** Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

**[0054]** Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

**[0055]** The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 100 mg/kg. of body weight daily are administered to patients and animals, e.g., mammals, to obtain effective release of growth hormone.

**[0056]** The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

EXAMPLE 16

N-[1(R)-[1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

Step A: methyl α(R)-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-3[(2',6'-difluorophenyl)-methoxy]propanic acid

**[0057]** Oil free sodium hydride (prepared from 60% oil dispersion of sodium hydride by washing with hexanes (3X), 1.2 g, 30.0 mmole), suspension in 30 mL N,N-dimethylformamide was added N-t-butyloxycarbonyl-(D)-serine (3.07 g, 15.0 mmole) in 10 mL N,N-dimethylformamide at room temperature. When no more gas evolves 2,6-diflorobenzyl bromide (2.68 g, 12.9 mmole) was added. After 18 hours stirring at room temperature, iodomethane (1.0 mL, 16.0 mmole) was added to the reaction mixture. The mixture was stirred another 1 hour, and then poured into water, and extracted with ethyl ether. The organic layer was washed sequentially with water (5X), brine and dried over sodium sulfate, filtered and concentrated. The residue was dissolved in 20 ml of chloroform and BOC-α-methylalanine, EDC, HOBT, and $Et_3N$ were added at room temperature. After 3 hours the reaction mixture was poured into water and extracted with methylene chloride. The organic layer was dried over sodium sulfate and concentrated. The title compound was obtained after purification by chromatography, (hexane/ethyl acetate:3/1) to give 2.37 g (35%).
$^1H$ NMR (300 MHz, $CDCl_3$ mixture of rotamers): 7.27 (m, 1 H), 7.02-6.88 (m, 2 H), 4.95 (m, 1 H), 4.72 (dt, 8, 3 Hz, 1 H), 4.58 (br. s, 2 H), 3.90 (m, 1 H), 3.78 (s, 1 H), 3.69 (s, 3 H), 1.48 (s, 3 H), 1.45 (s, 3 H), 1.41 (s, 9 H).

Step B: N-[1(R)-[1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

**[0058]** A solution of the intermediate obtained from this Example, Step A (2.37 g, 5.29 mmole) in 30 mL of methanol was added lithium hydroxide (340 mg, 8.1 mmole) in 3 mL of water. After 2 hours stirring at room temperature, the reaction mixture was concentrated, and then diluted with water, extracted with ethyl ether. The organic layer was discarded. The aqueous layer was acidified with 1 N hydrochloric acid to pH=1.5 and extracted with ethyl ether (3X). The organic layer was dried over sodium sulfate, filtered, and concentrated to give 2.18 g (95%) of acid. The title compound was prepared from acid (78 mg, 0.18 mmole), and 1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidine hydrochloride (50 mg, 0.165 mmole) by the procedure described in Example 20, Step B (use hydrochloride in ethyl ether

instead of trifluoroacetic acid) to give 48 mg (44%).
$^1$H NMR (400 MHz, $CD_3OD$ mixture of rotamers): 7.39 (m, 2 H), 7.22 (m, 1 1/2 H), 7.03 (m, 3 1/2 H), 5.14 (dd, 13, 7 Hz, 1 H), 4.66 (d, 16 Hz, 2 H), 4.49 (m, 1 H), 4.09 (m, 1 H), 3.92 (br. s, 2 H), 3.76 (m, 2 H), 3.25 (m, 1 H), 2.97 (s, 3/2 H), 2.96 (s, 3/2 H), 2.87 (m, 1 H), 1.95 (m, 1 H), 1.76 (m, 3 H), 1.61 (s, 3/2 H), 1.57 (s, 3 3/2 H), FAB-MS: 565 (M+1).

EXAMPLE 17

N-[1(R)-[(1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methylpropanamide hydrochloride

Step A: t-butyloxycarbonyl-(D)-hexahydrohomophenylalanine

**[0059]** A solution of t-butyloxycarbonyl-(D)-homophenylalanine (100 mg, 0.358 mmole) in 1 mL acetic acid was hydrogenated over $PtO_2$ at one atmosphere for 16 hours. The mixture was filtered through Celite and the filtrate concentrated and azeotroped with toluene.
$^1$H NMR (400 MHz, $CDCl_3$): 5.03 (d, 8 Hz, 1 H), 4.22 (m, 1 H), 1.82 (m, 1 H), 1.64 (m, 6 H), 1.41 (s, 9 H), 1.20 (m, 6 H), 0.84 (m, 2 H).

Step B: benzyl α(R)-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-4-cyclohexylbutanoic acid

**[0060]** A solution of BOC-D-homaphenylalanine in acetic acid was hygrogenated over $PtO_2$ at one atmosphere for 16 hours. The mixture was filtered through celite and concentrated. To this residue (44 mg) in 15 mol DMF was added benzyl bromide (198 ml) and $K_2CO_3$ (970 mg) at room temperature. After stirring overnight, the mixture was poured into 200 ml of ether and washed with water. The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, 7.5% ethyl acetate in hexanes) to provide 534 mg (95%) of this intermediate. A solution of 534 mg of this material in 10 ml 1:1 TFA/$CH_2Cl_2$ was stirred for 1 hour then stripped and azeotroped from toluene. The residue was dissolved in 10 ml $CH_2Cl_2$ and cooled to 0°C. BOC-α-methylalanine (362 mg), EDC, HOBT and NMM were added and stirred overnight. The solution was poured into 250 ml ethyl acetate and washed sequentially with 1N $NaHSO_4$ (aq.), water and saturated aqueous $NaHCO_3$. The organic phase was dried, filtered and concentrated. Purified by flash chromatography (silica gel, ethyl acetate/hexanes) to provide 638 mg of the title compound.
$^1$H NMR (200 MHz, $CDCl_3$): .8-.95 (m, 3 H), 1.05-1.3 (m, 7 H), 1.4-1.9 (m, 19 H), 2.15 (m, 2 H), 4.59 (m, 1 H), 4.87 (m, 1 H), 5.18 (m, 2 H), 6.96 (m, 1 H), 7.35 (m, 5 H). FAB-MS calculated for $C_{26}H_{40}N_2O_5$ 460; found 461.5 (M+H).

Step C: N-[1(R)-[(1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methylpropanamide hydrochloride

**[0061]** A mixture of 638 mg of the intermediate obtained in Step B and 100 mg of 10% Pd on carbon was stirred under a balloon containing $H_2$ for 4 hours. The mixture was filtered through Celite and the filtrate was concentrated. A portion (87 mg) of this residue was dissolved in 2 ml $CH_2Cl_2$ and 49.8 mg of 1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidine hydrochloride, EDC and HOBT were added and stirred for 16 hours. The solution was poured into 200 ml ethyl acetate and washed sequentially with 1N $NaHSO_4$ (aq.), water and saturated aqueous $NaHCO_3$. The organic phase was dried, filtered and concentrated. Purified by flash chromatography (silica gel, 60% ethyl acetate/hexanes) to provide 55 mg (47%) of this intermediate. All of this material was dissolved in 2 ml 1:1 TFA/$CH_2Cl_2$ and stirred for 1/2 hour. The solution was stripped and the residue was purified by flash chromatography (silica gel, methanol, $NH_4OH$(aq.), $CH_2Cl_2$). The compound was then dissolved in $CH_2Cl_2$, treated with HCl in ether and concentrated to provide the title compound.
$^1$H NMR (400 MHz, $CD_3OD$): .93 (m, 2 H), 1.15-1.3 (m, 6 H), 1.55-1.8 (m, 1 H), 2.06 (dt, 15, 4 Hz, 1 H), 2.88 (m, 1 H), 2.97 (m, 1 H), 3.35 (m, 2 H), 3.8-4.1 (m, 3 H), 4.51 (m, 1H), 4.83 (m, 1H), 7.06 (q, 7 Hz, 1H), 7.22 (m, 2H), 7.37 (d, 8 Hz, 1H).
FAB-MS calculated for $C_{27}H_{42}N_4O_4S$ 518; found 519.7 (M+H)

EXAMPLE 18 (METHOD 1)

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

Step A: 1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdine]hydrochloride

**[0062]** To a solution of 1.20 g (5.8mmol) of 1'-methyl-1,2-dihydro-spiro[3H-indole-3,4'-piperdine] (prepared as described in H. Ong et al *J. Med. Chem.* **1983,** *23*, 981-986) in 20 mL of dry dichloromethane at 0°C was added triethylamine (0.90 mL; 6.4 mmol) and methanesulfonyl chloride (0.49 mL; 6.35 mmol) and stirred for 30 min. The reaction mixture was poured into 15 mL of saturated aqueous sodium bicarbonate solution and extracted with dichloromethane (2X10 mL). The combined organics were washed with brine (20 mL), dried over anhydrous potassium carbonate, filtered and the solvent removed under reduced pressure to yield 1.44 g of the methanesulfonamide derivative as pale yellow oil which was used without purification.

**[0063]** To a solution of above crude product in 20 mL of dry 1,2-dichloroethane at 0°C was added 1.0 mL (9.30 mmol) of 1-chloroethyl chloroformate, and then stirred at RT for 30 min and finally at reflux for 1h. The reaction mixture was concentrated to approximately one third of the volume and then diluted with 20 mL of dry methanol and refluxed for 1.5h. The reaction was cooled to RT and concentrated to approximately one half of the volume. The precipitate was filtered and washed with a small volume of cold methanol. This yielded 1.0 g of the piperidine HCl salt as a white solid. The filtrate was concentrated and a small volume of methanol was added followed by ether. The precipitated material was once again filtered, washed with cold methanol, and dried. This gave an additional 0.49 g of the desired product. Total yield 1.49 g (70%).

$^1$H NMR($CDCl_3$, 200MHz) δ 7.43-7.20 (m, 3H), 7.10 (dd, 1H), 3.98 (bs, 2H), 3.55-3.40 (bd, 2H), 3.35-3.10 (m, 2H), 2.99 (s, 3H), 2.15 (t, 2H), 2.00 (t, 2H).

Step B: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-[(1,1-dimethylethoxy)carbonyl]amino-2-methylpropanamide

**[0064]** To 0.35g (1.15 mmol) of (2R)-2-[(1,1-dimethylethoxy)-carbonyl]amino-3-[2-(phenylmethyloxy)ethyl]-1-propanoic acid in 13 mL of dichloromethane was added 1,2-dihydro-1-methanesulfonylspiro-[3H-indole-3,4'-piperdine] hydrochloride (0.325 g; 1.07 mmol), 0.18 mL (1.63 mmol) of N-methylmorpholine, 0.159 g (1.18 mmol) of 1-hydroxybenztriazole(HOBT) and stirred for 15 min. EDC (0.31 g; 1.62 mol) was added and stirring was continued for 1h. An additional 60 µL of N-methylmorpholine was added and stirred for 45 min. The reaction mixture was poured into 5 mL of water and the organic layer was separated. The organic layer was washed with 5 mL of 0.5N aqueous hydrochloric acid and 5 mL of saturated aqueous sodium bicarbonate solution. The combined organics were dried over anhydrous magnesium sulfate, and concentrated to yield 0.627 g of the product as a yellow foam which was used without purification.

**[0065]** To a 0.627 g (1.07 mmol) of the above product in 5 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and stirred at RT for 75 min. An additional 1.00 mL of trifluoroacetic acid was added and stirred for 10 min. The reaction mixture was concentrated, diluted with 5.0 mL of dichloromethane and carefully basified by pouring into 10 mL of 10% aqueous sodium carbonate solution. The organic layer was separated and the aqueous layer was further extracted with 2X15 mL of dichloromethane. The combined organics were washed with 5 mL of water, dried over potassium carbonate, filtered and concentrated to give the 0.486 g of the amine as a light yellow foam which was used without purification.

**[0066]** To 0.486 g (1.01 mmol) of the amine and 10 mL of dichloromethane was added 0.26g (1.28 mmol) of 2-[(1,1-dimethylethoxy)carbonyl]amino-2-methyl-propanoic acid, 0.173 g (1.28 mmol) of 1-hydroxybenztriazole (HOBT) and EDC (0.245 g; 1.28 mol) and stirried at RT overnight. The reaction mixture was poured into 5.0 mL of water and the organic layer was separated. The aqueous layer was back extracted with 5 mL of dichloromethane. The combined organics were washed with 5.0 mL of 0.5N aqueous hydrochloric acid, 5 mL of saturated aqueous sodium bicarbonate solution dried over anhydrous magnesium sulfate, and concentrated to yield 0.751 g of the crude product as a yellow foam. A solution of this crude product in dichloromethane was chromatographed on 25 g of silica gel and eluted first with hexanes/acetone/dichloromethane (70/25/5) and then with hexanes/acetone/dichloromethane (65/30/5). This gave 0.63 g of the title compound as a white solid.

$^1$H NMR($CDCl_3$, 400MHz) Compound exists as a 3:2 mixture of rotamers δ 7.40-7.10 (m, 6H), 7.06 (d, 1/3H), 7.02 (t, 1/3H), 6.90 (t, 1/3H), 6.55 (d, 1/3H), 5.15 (m, 1H), 4.95 (bs, 1H), 4.63 (bd, 1/3H), 4.57-4.40 (m, 2 2/3 H), 4.10 (bd, 1/3H), 4.00 (bd, 1/3H), 3.82 (t, 1H), 3.78-3.62 (m, 2H), 3.60-3.50 (m, 1H), 3.04 (q, 1H), 2.87 (s, 1H), 2.86 (s, 2H), 2.80-2.60 (m, 1H), 1.90 (bs, 1H), 2.85-2.75 (m, 1H), 1.82-1.60 (m, 3H), 1.55-1.45 (m, 1H), 1.45 (s, 4H), 1.42 (s, 2H), 1.39 (s, 9H).

Step C: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

**[0067]** To 0.637 g (0.101 mmol) of the intermediate from Step B in 5 mL of dichloromethane was added 2.5 mL of trifluoroacetic acid and stirred at RT for 30 min. The reaction mixture was concentrated to an oil, taken up in 10 mL of ethyl acetate and washed with 8 mL of 10% aqueous sodium carbonate solution. The aqueous layer was further extracted with 5 mL of ethyl acetate. The combined organics were washed with 10 mL of water, dried over magnesium sulfate, filtered and concentrated to give the 0.512 g of the free base as a white foam.

**[0068]** To 0.512 g of the free base in 5 mL of ethyl acetate at 0°C was added 0.2 mL of saturated hydrochloric acid in ethyl acetate and stirred for 1.5 h. The white precipitate was filtered under nitrogen, washed with ether, and dried to give 0.50 g of the title compound as a white solid

$^1$H NMR (400MHz, $CD_3OD$) Compound exists as 3:2 mixture of rotamers. δ 7.40-7.28 (m, 4H), 7.25-7.17 (m, 2H), 7.08 (t, 1/3H), 7.00 (t, 1/3H), 6.80 (d, 1/3H), 5.16 (ddd, 1H), 4.60-4.42 (m, 3H), 4.05 (t, 1H), 3.90 (bs, 2H), 3.83-3.70 (m, 2H), 3.30-3.15 (m, 1H0, 2.97 (s, 1H), 2.95 (s, 2H), 2.90-2.78 (m, 1H), 1.96 (t, 1/3H), 1.85-1.65 (m, 4H), 1.63 (s, 2H), 1.60 (s, 4H).

EXAMPLE 19 (METHOD 2)

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl) carbonyl] -2-(phenylmethyloxy)ethyl] -2-amino-2-methylpropanamide hydrochloride

Step A: (2R)-[[[-2-(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl] amino-2-(phenylmethoxy) ethyl]-1-propanoic acid allyl ester

**[0069]** Prepared from (2R)-2-[(1,1-dimethylethoxy)carbonyl]-amino-3-(phenylmethyloxy)ethyl-propanoic acid and allyl alcohol by carrying out the coupling reaction in $CH_2Cl_2$ in the presence of EDC and DMAP.

$^1$H NMR (400MHz, $CDCl_3$) δ 7.25 (s, 5H), 5.8 (m, 1H), 5.2 (dd, 2H), 5.0 (bs, 1H), 4.7 (m, 1H), 4.6 (m, 2H), 4.4 (dd, 2H), 3.9 (dd, 1H), 3.6 (dd, 1H), 1.45 (d, 6H), 1.39 (s, 9H).

Step B: (2R)-[[[-2-(1,1-dimethylethoxy)carbonyl] amino]-2,2-dimethyl-1-oxoethyl]amino-2-(phenylmethyloxy) ethyl)-1-propanoic acid

**[0070]** To a stirred solution of the crude intermediate obtained in Step A (6.7 g, 15.9 mmol), tetrakis (triphenylphosphine)-palladium (1.8 g, 0.1 eq) and, triphenyl phosphine (1.25 g, 0.3 eq) was added a solution of potassium-2-ethyl hexanoate (35 mL, 0.5M solution in EtOAc). The reaction mixture was stirred at room temperature under nitrogen atmosphere for lh and then diluted with ether (100 mL) and poured into ice-water. The organic layer was seperated and the aqueous fraction was acidified with citric acid (20%), then extracted with EtOAc. The EtOAc extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated to give the title compound as a solid.

$^1$H NMR (400Hz, $CD_3OD$) δ 7.3 (s, 5H), 4.7 (m, 1H), 4.5 (s, 2H), 4.0 (m, 1H), 3.6 (m, 1H), 1.4 (d, 6H), 1.3 (s, 9H).

Step C: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-[(1,1-dimethyl-ethoxy)carbonyl]amino-2-methylpropanamide

**[0071]** To a solution of 1.0 g (3.44 mmol) of 1-methanesulfonylspiro[indoline-3,4'-piperidine] hydrochloride, 1.44 g (3.78 mmol) of (2R)-[[-2-(1,1-dimethylethoxy)carbonyl)amino]-2,2-dimethyl-1-oxoethyl]-amino-2-(phenylmethyloxy) ethyl)-1-propanoic acid, N-methyl morpholine (0.58 mL; 5.20 mmol), and 1-hydroxybenztriazole (HOBT) (0.58 g; 3.78 mmol), in 50 mL of dichloromethane was added EDC (1.03 g; 5.20 mmol) and stirred at RT for 16h. The reaction mixture was diluted with an additional 50 mL of dichloromethane and washed with aqueous sodium bicarbonate solution (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Flash chromatography (50 g silica gel) of the crude oily residue gave 2.148 g (90%) of the desired material as a colorless foam.

$^1$H NMR ($CDCl_3$, 400MHz) Compound exists as a 3:2 mixture of rotamers δ 7.40-7.10 (m, 6H), 7.06 (d, 1/3H), 7.02 (t, 1/3H), 6.90 (t, 1/3H), 6.55 (d, 1/3H), 5.15 (m, 1H), 4.95 (bs, 1H), 4.63 (bd, 1/3H), 4.57-4.40 (m, 2 2/3 H), 4.10 (bd, 1/3H), 4.00 (bd, 1/3H), 3.82 (t, 1H), 3.78-3.62 (m, 2H), 3.60-3.50 (m, 1H), 3.04 (q, 1H), 2.87 (s, 1H), 2.86 (s, 2H), 2.80-2.60 (m, 1H), 1.90 (bs, 1H), 2.85-2.75 (m, 1H), 1.82-1.60 (m, 3H), 1.55-1.45 (m, 1H), 1.45 (s, 4H), 1.42 (s, 2H), 1.39 (s, 9H).

Step D: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

**[0072]** To a solution of 2.148 g (3.41 mmol) of the intermediate from Step C in 10 mL of dichloromethane was added 5 mL of trifluoroacetic acid and stirred for 1h. The reaction mixture was concentrated and basified with 100 mL of 5% aqueous sodium carbonate solution and extracted with dichloromethane (3X50 mL). The combined organics were washed with brine (50 mL), dried over anhydrous potassium carbonate, filtered, and concentrated to yield a colorless foam. To a solution of the foam in 25 mL of ethyl acetate at 0°C was added 4 mL of 1M solution of hydrochloric acid in ethyl acetate. The precipitate was filtered and washed first with ethyl acetate and then with ethyl acetate-ether (1:1), dried to yield 1.79 g (93%) of the title compound as a colorless solid.
$^1$H NMR(400MHz, $CD_3OD$) Compound exists as 3:2 mixture of rotamers. δ 7.40-7.28 (m, 4H), 7.25-7.17 (m, 2H), 7.08 (t, 1/3H), 7.00 (t, 1/3H), 6.80 (d, 1/3H), 5.16 (ddd, 1H), 4.60-4.42 (m, 3H), 4.05 (t, 1H), 3.90 (bs, 2H), 3.83-3.70 (m, 2H), 3.30-3.15 (m, 1H0, 2.97 (s, 1H), 2.95 (s, 2H), 2.90-2.78 (m, 1H), 1.96 (t, 1/3H), 1.85-1.65 (m, 4H), 1.63 (s, 2H), 1.60 (s, 4H).

EXAMPLE 20

N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-bromo-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy) ethyl]-2-amino-2-methylpropanamide trifluoroacetate

Step A: N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-bromo-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyl-oxy)-ethyl] -2-[(1,1-dimethylethoxy)-carbonyl]amino-2-methylpropanamide

**[0073]** To a solution 300 mg (1.03 mmol) of 1-methanesulfonylspiro-[3H-indole-3,4'-piperidine] hydrochloride in 5 mL of glacial acetic acid was added 0.28 g (2.06 mmol) of bromine and stirred at RT for 1h. The reaction mixture was concentrated to dryness, basified with 10 mL of 5% aqueous sodium carbonate solution, and extracted with dichloromethane (3X10 mL). The combined organics were washed with brine (10 mL), dried over anhydrous potassium carbonate, filtered, and concentrated to yield 0.25 g of a crude product as a yellow oil which was used without purification.

Step B:

**[0074]** To a solution of the above crude product in 10 mL of dichloromethane was added 0.43 g (1.13 mmol) of the intermediate from Example 19 Step B, 0.17 g (1.13 mmol) of HOBT, and 0.34 g (1.70 mmol) of EDC and stirred at RT for 16h. The reaction mixture was diluted with 15 mL of ether and washed with 10% aqueous citric acid (15 mL), saturated sodium bicarbonate solution (15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to give a crude oily product. This residue was purified was flash chromatography (15 g $SiO_2$; $CH_2Cl_2$-Acetone(10:1) as eluent) to yield 0.184 g (26% for 2 steps) of the coupled material as colorless foam.
**[0075]** To 0.184 g (0.26 mmol) of the above material in 2 mL of dichloromethane was added 2 mL of trifluoroacetic acid and stirred at RT for 1h. The reaction mixture was evaporated to dryness to yield 0.146 g (93%) of the title compound as a white solid.
FAB-MS: calculated for $C_{27}H_{34}BrN_4O_5S$ 608; found 609.5

EXAMPLE 21

N-[1(R)-[(1,2-Dihydro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide dihydrochloride

Step A: Spiro[3H-indole-3,4'-piperidine]

**[0076]** To a solution of 1.0 g (5.0 mmol) of 1'-methyl-spiro[3H-indole-3,4'-piperidine] (prepared as described in H. Ong et al *J. Med. Chem.* **1983**, *23,* 981-986) and 1.0 g of powdered potassium carbonate in 30 mL of dry dichloromethane at RT was added to 0.50 g of cyanogen bromide and stirred for 1h. The reaction mixture was filtered through a pad of celite and washed with chloroform-methanol (95:5). The filtrate was concentrated and the residue was flushed through a pad of silica gel with chloroform-methanol (95:5) as eluent. This gave ~1.2 g of a yellow oil which was used without purification.
**[0077]** To a suspension of above compound in 30 mL of dry DME at 0°C was added 0.30 g of lithium aluminum hydride and warmed to RT and finally refluxed for 1h. The reaction mixture was cooled to 0°C and quenched with 0.30

mL of water, 0.30 mL of 15% aqueous of sodium hydroxide solution, and 0.90 mL of water. The solids were filtered off through a pad of celite and washed well with chloroform-methanol (10:1). Concentration of the filtrate gave 0.74 g of the compound as a yellow foam. This material was a 1:1 mixture of the title compound and 1'-methyl-spiro[3H-indole-3,4'-piperidine] .

Step B: (2R)-[[-2-[[1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-1H-indole-3-propanoic acid benzyl ester

**[0078]** To 5.0 g (16.5 mmol) of the commercially available N-t-BOC-D-tryptophan in 100 mL of chloroform was added 1.80 mL (16.5 mmol) of benzyl alcohol, 0.20 g (1.65 mmol) of 4-N,N-dimethylamino pyridine (DMAP), and 3.20 g of EDC and stirred for 16h. The reaction mixture was poured into 100 mL of water and the organic layer was seperated. The aqueous was further extracted with 2X100 mL of chloroform. The combined organics were washed with 50 mL of 10% aqueous citric acid, 100 mL of 10% aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered and concentrated to give a thick oil.

**[0079]** To a solution of this oil in 10 mL of dichloromethane was added 20 mL of trifluoroacetic acid and stirred for 1h. The reaction mixture was concentrated, basified carefully with saturated aqueous sodium bicarbonate solution, and extracted with chloroform (2X100 mL). The combined organics were washed with brine (100 mL), dried over potassium carbonate, filtered, and concentrated to give 5.46 g of the amine as a brown oil which was used without purification.

**[0080]** To 5.46 g of the above product in 100 mL of chloroform was added 3.40 g (22.2 mmol) of HOBT, 4.60 g (22.2 mmol) of N-BOC-α-methyl alanine, and 5.32 g (28.0 mmol) of EDC and stirred for 16h. The reaction mixture was poured into 100 mL of water and the organic layer was seperated. The aqueous was further extracted with 2X100 mL of chloroform. The combined organics were washed with 50 mL of 10% aqueous citric acid, 100 mL of 10% aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered and concentrated to give 6.94 g of the product as a thick oil. Flash chromatography (200 g $SiO_2$; hexane-ethyl acetate as eluent) gave 4.75 g of the desired material as a colorless foam.
$^1$H NMR ($CDCl_3$, 200MHz) δ 8.48 (bs, 1H), 7.54 (bd, 1H), 7.38-7.23 (m, 3H), 7.19 (bd, 2H), 7.15-7.00 (m, 1H), 6.90 (d, 1H), 6.86 (d, 1H), 5.06 (bs, 2H), 4.95 (ddd, 1H), 3.30 (2dd, 2H), 1.40 (s, 15H)

Step C: (2R)-[[-2-[[1,1-dimemylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-1H-indole-3-propanoic acid

**[0081]** To a solution of 4.75 g of the material from Step B in 100 mL of ethanol was added 1.0 g of 10% Pd/C and stirred at RT under a $H_2$ balloon for 18h. The catalyst was filtered off through a pad of celite and washed with ethyl acetate. The filtrate was concentrated to give 2.96 g of the acid as a colorless foam.
$^1$H NMR ($CDCl_3$, 200MHz) δ 8.60 (bs, 1H), 7.55 (d, 1H), 7.26-6.90 (m, 3H), 6.88 (bd, 1H), 4.80 (m, 1H), 3.32 (2dd, 2H), 1.37 (s, 3H), 1.35 (s, 12H)

Step D: N-[1(R)-[(1,2-Dihydro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-[(1,1-dimethylethoxy)-carbonyl]amino-2 -methylpropanamide

**[0082]** To a solution of 0.122 g (0.542 mmol) of a 1:1 mixture of the intermediate from step A and 1'-methyl-spiro[3H-indole-3,4'-piperidine] in 5 mL of dry chloroform at RT was added 0.105 g (0.271 mmol) of the intermediate from Step C, 41 mg (0.271 mmol) of HOBT, and 80 mg (0.41 mmol) of EDC and stirred at RT for 2h. The reaction mixture was diluted with 10 mL of chloroform was washed with saturated aqueous sodium bicarbonate solution (10 mL) and 10 mL of brine, dried over anhydrous potassium carbonate, filtered and concentrated. Flash chromatography (10 g $SiO_2$; 2% MeOH-$CHCl_3$) of the residue gave 94 mg of the desired product as a yellow foam.

**[0083]** The compound exists as 3:2 mixture of rotamers. $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.37 (d, 1/3H), 8.35 (d, 2/3H), 8.19 (d, 1H), 7.72 (d, 2/3H), 7.60 (d, 1/3H), 7.38 (d, 2/3H), 7.32 (d, 1/3H), 7.22-7.08 (m, 3H), 7.00 (2t, 1H), 6.93 (d, 1/3H), 6.69 (t, 1H), 6.60 (d, 1/3H), 6.56 (d, 2/3H), 6.50 (d, 2/3H), 5.30-5.15 (m, 1H), 5.00 (bs, 1H), 4.34 (m, 1H), 3.62-3.50 (m, 1H), 3.30-3.11 (m, 4H), 2.90 (dt, 1H), 2.40 (dt, 1/3H), 1.70-1.55 (m, $1^{2/3}$H), 1.34 (s, 2H), 1.31 (s, 4H), 1.28 (s, 1H), 1.31 (s, 9H), 1.20-1.11 (m, 1H), 0.32 (dt, 1/3H)

Step E: N-[1(R)-[(1,2-Dihydro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide dihydrochloride

**[0084]** To 27.5 mg of the intermediate from Step D was added 1.0 mL of methanol and 1.0 mL of concentrated hydrochloric acid and stirred at RT for 1h. The reaction mixture was concentrated, basified with 5 mL of 10% aqueous

sodium carbonate solution, and extracted with chloroform (3X5 mL). The combined organics were washed with brine (10 mL), dried over potassium carbonate, filtered, and concentrated to yield a thick oil. Preparative TLC (0.50 mm plate; chloroform-methanol 96:5+1% $NH_4OH$) gave 12 mg of the desired product as a yellow solid.
The compound exists as 3:2 mixture of rotamers. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.37 (d, 1/3H), 8.35 (d, 2/3H), 8.19 (d, 1H), 7.72 (d, 2/3H), 7.60 (d, 1/3H), 7.38 (d, 2/3H), 7.32 (d, 1/3H), 7.22-7.08 (m, 3H), 7.00 (2t, 1H), 6.93 (d, 1/3H), 6.69 (t, 1H), 6.60 (d, 1/3H), 6.56 (d, 2/3H), 6.50 (d, 2/3H), 5.30-5.15 (m, 1H), 4.34 (m, 1H), 3.62-3.50 (m, 1H), 3.30-3.11 (m, 4H), 2.90 (dt, 1H), 2.40 (dt, 1/3H), 1.70-1.55 (m, $1^{2/3}H$), 1.34 (s, 2H), 1.31 (s, 4H), 1.28 (s, 1H), 1.20-1.11 (m, 1H), 0.32 (dt, 1/3H).

EXAMPLE 22

N-[1(R)-[(1,2-Dihydro-1-methylcarbonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

**[0085]** To 26 mg of the intermediate from Example 21, Step D in 1.0 mL of 1,2-dichloroethane and 55 µL (0.14 mmol) of N-methylmorpholine at 0°C was added 6.6 µL (0.93 mmol) of acetyl chloride and stirred for 1h. The reaction mixture was diluted with 5 mL of ether, washed with 5 mL of 10% aqueous citric acid, 5 mL of saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered, and concentrated to give a pale yellow foam which was used without purification.

**[0086]** To the above material in 1.0 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and stirred at RT for 1h. The reaction mixture was concentrated, basified with 5 mL of 10% aqueous sodium carbonate solution, and extracted with chloroform (3X5 mL). The combined organics were washed with brine (10 mL), dried over potassium carbonate, filtered, and concentrated to yield a thick oil. To a solution of this material in 1.0 mL of methanol was added 1.0 mL of 4M hydrochloric acid in dioxane and concentrated to dryness to yield 16 mg of the title compound as a pale yellow solid.
The compound exists as a 3:2 mixture of rotamers. $^1H$ NMR ($CD_3OD$, 400MHz) δ 8.43 (d, 1H), 8.35 (t, 1H), 7.72 (d, 2/3H), 7.61 (d, 1/3H), 7.40-7.25 (m, 2H), 7.20-7.08 (m, 3H), 7.05-6.95 (m, $2^{2/3}H$), 6.50 (d, 1/3H), 5.25-5.10 (m, 1H), 5.00-4.84 (2bd, 1H), 3.68-3.45 (m, 3H), 3.20 (m, 2H), 2.60-2.48 (m, $1^{1/3}H$), 2.30 (dt, 1/3H), 2.00 (s, 1H), 1.98 (s, 2H), 1.81-1.40 (m, 4H), 1.35 (s, 2H), 1.33 (s, 2H), 1.32 (s, 1H), 1.30 (s, 1H), 1.25-1.15 (m, 1H), 1.10-1.00 (m, 1H), 0.20 (dt, 1/3H)

EXAMPLE 23

N-[1(R)-[(1,2-Dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide

**[0087]** To 26 mg (0.050 mmol) of the intermediate from Example 21, Step D in 1.0 ml of 1,2-dichloroethane and 5 µl of N-methyl morpholine was added at 0°C 7.5 µL of benzenesulfonyl chloride and stirred for 1h. The reaction mixture was diluted with 10 ml of ether washed with 5 ml of 10% aqueous citric acid, 5 ml of saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 29.8 mg of a crude product as a pale yellow foam. To a solution of this material in 2 ml of methanol was added 1.0 ml of conc. hydrochloric acid and stirred for 1h. The solvent were removed under reduced pressure to yield the title compound as a brown solid.
This compound exists as a 3:2 mixture of rotamers. $^1H$ NMR($CDCl_3$, 400MHz) δ 8.30 (bs, 1/3H), 8.20 (bs, 2/3H), 8.05 (bs, 2/3H), 7.88 (d, 1/3H), 7.72-7.45 (m, 5H), 7.43-7.30 (m, 4H), 7.20-7.05 (m, 2H), 7.00-6.90 (m, $2^{2/3}H$), 6.35 (d, 1/3H), 5.25-5.10 (m, 1H), 4.90 (bs, 1H), 4.30 (dt, 1H), 4.15 (dt, 1H), 3.95 (dd, 1H), 3.60-3.40 (m, 3H), 3.25-3.20 (m, 2H), 2.90 (dt, 1H), 2.73 (dt, $2^{2/3}H$), 2.35 (m, $1^{1/3}H$), 1.80 (m, 1H), 1.50 (s, 1H), 1.43 (s, 2H), 1.39 (s, 3H), 1.30-1.20 (m, 2H), 1.00 (bd, 1/3H), 0.90-0.70 (m, 2H), 0.55 (bd, 1/3H), 0.48 (dd, 2/3H), -0.90 (dt, 1/3H)

EXAMPLE 24

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

**[0088]** To a solution of 0.258 g (0.50 mmol) of the intermediate from Example 21, Step D in 10 mL of dry dichloromethane at 0°C was added 0.39 mL(1.00 mmol) of N-methyl morpholine, and 45 µL (0.60 mmol) of methanesulfonyl chloride and stirred for 30 min. The reaction was diluted with 10 mL of ether and washed with saturated sodium bicarbonate solution (5 mL), brine (5 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to yield the product as a pale yellow foam which was used without purification. To a solution of this material in 3.0 mL of dichlo-

romethane was added 1.0 mL of trifluoroacetic acid and stirred at RT for 1h. The reaction mixture was concentrated, basified with 5 mL of 10% aqueous sodium carbonate solution, and extracted with chloroform (3X5 mL). The combined organics were washed with brine(10 mL), dried over potassium carbonate, filtered, and concentrated to yield a thick oil. To a solution of this material in 3.0 mL of methanol was added 200 µL of 4M hydrochloric acid in dioxane and concentrated to dryness to yield 98 mg of the desired material as a pale yellow solid.
The compound exists as a 3:2 mixture of rotamers. $^1$H NMR ($CD_3OD$, 400MHz) δ 8.43 (d, 1H), 8.35 (t, 1H), 7.72 (d, 2/3H), 7.61 (d, 1/3H), 7.40-7.25 (m, 2H), 7.20-7.08 (m, 3H), 7.05-6.95 (m, $2^{2/3}$H), 6.50 (d, 1/3H), 5.25-5.10 (m, 1H), 5.00-4.84 (2bd, 1H), 3.68-3.45 (m, 3H), 3.20 (m, 2H), 2.82 (s, 1H), 2.80 (s, 2H), 2.60-2.48 (m, $1^{1/3}$H), 2.30 (dt, 1/3H), 1.81-1.40 (m, 4H), 1.35 (s, 2H), 1.33 (s, 2H), 1.32 (s, 1H), 1.30 (s, 1H), 1.25-1.15 (m, 1H), 1.10-1.00 (m, 1H), 0.20 (dt, 1/3H)

EXAMPLE 25

N-1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-[3-phenylpropyl]-2-amino-2-methylpropanamide hydrochloride

Step A: N-1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-[(1,1-dimethylethoxy)carbonyl]amino-2-methylpropanamide

**[0089]** The title compound was prepared from (2R)-2-[(1,1-dimethylethoxy)carbonyl]amino-4-phenyl-1-butanoic acid and 1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidine] hydrochloride by using the coupling method as described in Example 18, Step B. The crude product was purified on silica gel using 5% Acetone in $CH_2Cl_2$.
$^1$H NMR (400MHz, $CDCl_3$) δ 7.2 (m, 9H), 4.9 (m, 1H), 4.5 (m, 1H), 3.8 (m, 2H), 3.2 (m, 2H), 2.9 (s, 3H), 2.7 (m, 2H), 2.3 (s, 2H), 2.0 (m, 2H), 1.7 (m, 4H), 1.5 (s, 6H), 1.4 (s, 9H).

Step B: N-1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methylpropanamide hydrochloride

**[0090]** Prepared from the intermediate obtained in step A using the deprotection method as described in Example 18, Step C.
$^1$H NMR (400MHz, $CD_3OD$) δ 7.3 (m, 9H), 4.5 (m, 1H), 3.9 (m, 2H), 3.5 (m, 2H), 3.2 (m, 2H), 2.9 (s, 3H), 2.7 (m, 4H), 2.0 (m, 4H), 1.6 (s, 6H).

EXAMPLE 26

N-[1(R)-[(1,2-Dihydro-1-trifluoromethanesulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

Step A: 1,2-Dihydro-1-benzyloxycarbonyl--5-fluoro-spiro[3H-indole-3,4'-piperdine]

**[0091]** To 7.82 g of 60% sodium hydride was added hexane and the liquids were decanted. To this was added a solution of 11.10 mL(89 mmol) of 2,5-difluorophenylacetonitrile in 150 mL of DMSO and stirred for 30 min. A solution of 15.10 g of 1-chloromethyl ethylamine hydrochloride in 150 mL of DMSO was added dropwise and heated at 75°C for 4h. The reaction mixture was poured into 600 g of ice and extracted with ether (5X200 mL). The combined organics were washed with 3X100 mL of 2N hydrochloric acid. The combined aqueous extracts were basified to pH=9 with 50% aqueous sodium hydroxide and extracted with ether (3X200 mL). The combined organics were washed with brine (100 mL), dried over potassium carbonate and concentrated to give 15.54 g of a thick oil.
**[0092]** Ethanol (24 mL) was added in dropwise fashion to 9.90 g of lithium aluminum hydride in 250 mL of DME at 0°C and then warmed to reflux. A solution of the compound in 250 mL of DME was added and refluxed for 72h. The reaction was then cooled to 0°C and quenched with water (10 mL), 10 mL of 15% NaOH, and 30mL of water. The slurry was dried over $K_2CO_3$, filtered, and concentrated to give 13.6 g of a thick oil. This crude product was triturated with hexanes, the solid was filtered, and washed further with hexanes. 200MHz NMR ($CDCl_3$) of the solid (2.6 g) indicated about 75% of the desired spiro-indoline.
**[0093]** To a solution of 1.02 g of this mixture in 50 mL of $CH_2Cl_2$ at 0°C was added 1.0 mL of triethylamine and 0.80 mL of CBZ-Cl and stirred for 1h at RT. The reaction mixture was poured into 50 mL of 5% HCl and the aqueous layer was separated. The aqueous layer was basified with 50% NaOH to pH=10 and extracted with $CH_2Cl_2$ (3x25 mL). The combined organics were washed with brine (50 mL), dried over $K_2CO_3$, and concentrated to yield 1.26 g of the compound as a thick oil.

$^1$H NMR (200MHz, $CDCl_3$) δ 7.7-7.90 (m, 1H), 7.50-7.15 (m, 6H), 6.95-6.60 (m, 2H), 5.28 (bs, 2H), 3.90 (bs, 2H), 2.85 (bd, 2H), 2.30 (s, 3H), 2.20-1.80 (m, 4H), 1.65 (bd, 2H).

Step B: N-[1(R)-[(1,2-Dihydro-1-benzyloxycarbonyl-5-fluorospiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-[[(1,1-dimethylethyloxy)carbonyl] amino]-2-methylpropanamide

**[0094]** To 1.62 g (4.62 mmol) of the above intermediate from Step A in 10 mL of 1,2-dichloroethane at 0°C was added 0.65 mL of ACE-Cl and refluxed for 1h. The reaction mixture was concentrated to one-third the volume and diluted with 10 mL of methanol and heated to reflux for 1h. The reaction mixture was concentrated to dryness and triturated with ether to give brown solid. This material was dissolved in saturated sodium bicarbonate solution (25 mL), and extracted with dichloromethane (2X25 mL). The combined organics were dried over $K_2CO_3$ and concentrated to give 0.384 g of the free base.

**[0095]** To 0.384 g of this material in 15 mL of $CH_2Cl_2$ was added 0.483 g of the acid intermediate obtained from Step C of Example 21, 0.189 g of HOBT, and 0.34 g of EDC and stirred for 18h. The reaction mictured was poured into 10 mL of water and extracted with $CH_2Cl_2$ (2X10 mL). The combined organics were washed with 20 mL of 10% citric acid, 20 mL of saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. Flash chromatographed of the residue on 25 g of silica gel with hexanes-acetone (1:1) as eluent gave 0.389 g of the desired material.

$^1$H NMR (200MHz, $CDCl_3$) δ 7.7-7.90 (m, 1H), 7.50-7.15 (m, 6H), 6.95-6.60 (m, 2H), 5.28 (bs, 2H), 3.90 (bs, 2H), 2.85 (bd, 2H), 2.30 (s, 3H), 2.20-1.80 (m, 4H), 1.65 (bd, 2H).

Step C: N-[1(R)-[(1,2-Dihydro-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl] -[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methylpropanamide

**[0096]** To a solution of 0.363 g of the intermediate obtained from Step B in 5 mL of of ethanol was added 0.10g of 20% palladium hydroxide on carbon and hydrogenated under $H_2$ balloon for 1h. the catalyst was filtered off and washed with more methanol. The filtrate was concentrated to yield 0.262 g of the desired material.

$^1$H NMR (400MHz, $CDCl_3$) This material was 2:1 mixture of rotamers. δ 8.85-8.60 (2bs, 1H), 7.70(d, 2/3H), 7.55 (d, 1/3H), 7.38 (d, 2/3H), 7.30 (d, 1/3H), 7.28-7.15 (m, 4H), 7.13-7.02 (m, 2H), 6.65 (dt, 2H), 6.50 (dd, 1/3H), 6.45 (dd, 2/3H), 6.14 (dd, 2/3H), 5.30-5.13 (m, 1H), 5.10 (bs, 1H), 4.30 (bd, 2/3H), 422 (bd, 1/3H), 3.50-3.30 (m, 1H), 3.30-3.00 (m, 4H), 3.00-2.80 (m, 1H), 2.73 (t, 1H), 2.53-2.40 (m, 11/3H), 2.20 (t, 1/3H), 1.49 (s, 3H), 1.45 (s, 3H), 1.41 (s, 9H) 1.20 (dt, 1/3H), 0.95 (bd, 2/3H), 0.90 (dt, 2/3H), -0.05 (dt, 1/3H).

Step D: N-[1(R)-[(1,2-Dihydro-1-trifluoromethanesulfonyl-5-fluoro-spiro [3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3 -yl)ethyl]-[[(1,1-dimethylethyloxy)carbonyl] amino]-2-methylpropanamide

**[0097]** To a solution of 30 mg of the intermediate obtained from Step C in 1mL of dichloromethane at 0°C was added 0.050 mL of triethylamine and 0.020 mL of triflic anhydride and stirred for 5 min. the catalyst was filtered off and washed with more methanol. The reaction was poured into 5 mL of 5% aqueous sodium carbonate solution and stirred for 5 min. The aqueous layer was extracted with $CH_2Cl_2$ (2X5 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography of the residue on 3 g of silica gel with $CH_2Cl_2$-acetone (4:1) as eluent gave 21 mg of product.

$^1$H NMR (400MHz, $CDCl_3$) This material was 2:1 mixture of rotamers. δ 8.40 (bs, 2/3H), 8.25 (bs, 1/3H), 7.70(d, 2/3H), 7.60 (d, 1/3H), 7.40 (d, 2/3H), 7.35-7.10 (m, 5H), 6.90-6.80 (m, 2H), 6.18 (dd, 1H), 5.30-5.13 (m, 1H), 4.95(bs, 2/3H), 4.90 (s, 1/3H), 4.45 (bd, 2/3H), 4.35 (bd, 1/3H), 385-3.70 (m, 2H), 3.70-3.55 (m, 2H), 3.30-3.10 (m, 2H), 2.70 (t, 1H), 2.45 (t, 1/3H), 2.35 (t, 2/3H), 1.49 (s, 3H), 1.45 (s, 3H), 1.41 (s, 9H), 1.20 (dt, 1/3H), 0.95 (bd, 2/3H), 0.90 (dt, 2/3H), -0.05 (dt, 1/3H).

Step E: N-[1(R)-[(1,2-Dihydro-1-trifluoromethanesulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]--2-methylpropanamide trifluoroacetate

**[0098]** To a solution of 21 mg of the intermediate obtained from Step D was maintained in 1 mL of dichloromethane and 1 mL of trifluoroacetic acid at room temperature for 30 min. The volatiles were evaporated to dryness and triturated with ether to give a yellow solid.

$^1$H NMR (400MHz, $CD_3OD$) This material was 2:1 mixture of rotamers. δ 7.65(d, 2/3H), 7.60 (d, 1/3H), 7.42 (d, 2/3H), 7.35-7.10 (m, 5H), 6.93-6.80 (m, 2H), 6.24 (dd, 1H), 5.30-5.13 (m, 1H), 4.95(bs, 2/3H), 4.90 (s, 1/3H), 4.45 (bd, 2/3H), 4.35 (bd, 1/3H), 385-3.70 (m, 2H), 3.70-3.55 (m, 2H), 3.30-3.10 (m, 2H), 2.70 (t, 1H), 2.45 (t, 1/3H), 2.35 (t, 2/3H), 1.49 (s, 3H), 1.45 (s, 3H), 0.93 (bd, 2/3H), 0.90 (dt, 2/3H), -0.05 (dt, 1/3H).

EXAMPLE 27

N-[1(R)-[(1,2-Dihydro-1-[methoxycarbonyl]methylsulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

Step A: N-[1(R)-[(1,2-Dihydro-1-[methoxycarbonyl]methylsulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]]-1'-yl) carbonyl]-2-(indol-3-yl)ethyl]--2-methylpropanamide trifluoroacetate

**[0099]** To a solution of 77 mg of the intermediate obtained from Step C of Example 26 in 1 mL of dichloromethane at 0°C was added 0.30 mL of N-methylmorpholine, and 0.024 mL of 2-carbomethoxymethanesulfonylchloride and stirred for 1h. The reaction was poured into 5 mL of 5% aqueous sodium carbonate solution and stirred for 5 min. The aqueous layer was extracted with $CH_2Cl_2$ (2X5mL) and the combined organics were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography of the residue on 5g of silica gel with $CH_2Cl_2$-acetone (4:1) as eluent gave 64 mg of product.

$^1H$ NMR (400MHz, $CDCl_3$) This material was 2:1 mixture of rotamers. δ 8.48 (bs, 2/3H), 8.35 (bs, 1/3H), 7.70(d, 2/3H), 7.60 (d, 1/3H), 7.40 (d, 2/3H), 7.32 (d, 1/3H), 7.25-7.00 (m, 4H), 6.90-6.78 (m, 2H), 6.18 (dd, 1H), 5.30-5.20 (m, 1H), 4.97(bs, 2/3H), 4.91 (s, 1/3H), 4.50-4.35 (2bd, 1H), 4.02 (s, 2/3H), 3.99 (s, 1/3H), 3.76(q, 2H), 3.58 (s, 1H), 3.56 (s, 2H), 3.08-3.07 (m, 2H), 2.72 (t, 1H), 2.50-2.30 (2t, 1H), 1.65 (t, 1/3H), 1.50 (s, 2H), 1.46 (s, 4H), 1.40 (s, 9H), 1.30 (m, 1/3H), 1.10 (bd, 2/3H), 0.88 (dt, 2/3H), -0.13 (dt, 1/3H).

Step B: N-[1(R)-[(1,2-Dihydro-1-[methoxycarbonyl]methylsulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]]-1'-yl) carbonyl]-2-(indol-3-yl)ethyl]-2-methylpropanamide trifluoroacetate

**[0100]** To a solution of 24 mg of the intermediate obtained from Step A was maintained in 1 mL of dichloromethane and 1 mL of trifluoroacetic acid at room temperature for 30 min. The volatiles were evaporated to dryness and triturated with ether to give 23 mg of a colorless solid.

$^1H$ NMR (400MHz, $CD_3OD$) This material was 2:1 mixture of rotamers. δ 8.70 (bs, 1/3H), 8.60 (bs, 2/3H), 7.60(m, 2/3H), 7.50 (d, 2/3H), 7.48 (m, 1/3H), 7.40 (d, 2/3H), 7.31 (d, 1/3H), 7.25-7.00 (m, 4H), 6.95-6.85 (m, 1H), 6.70 (dd, 1/3H), 6.15 (dd, 2/3H), 5.20-5.10 (m, 1H), 4.38 (bd, 1/3H), 4.28 (bd, 2/3H), 4.02 (s, 2/3H), 3.99 (s, 1/3H), 3.76(q, 2H), 3.58 (s, 1H), 3.56 (s, 2H), 3.08-3.07 (m, 2H), 2.72 (t, 1H), 2.50-2.30 (2t, 1H), 1.65 (t, 1/3H), 1.65 (s, 2H), 1.60 (s, 4H), 1.30 (m, 1/3H), 1.00 (bd, 2/3H), 0.88 (dt, 2/3H), -0.10 (dt, 1/3H).

EXAMPLE 28

N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy) ethyl]-2-amino-2-methylpropanamide hydrochloride

Step A: N-[1(R)-[(1,2-Dihydro-1-benzyloxycarbonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methylpropanamide

**[0101]** To 0.330 g of the 1,2-Dihydro-1-benzyloxycarbonyl-5-fluoro-spiro[3H-indole-3,4'-piperdine] obtained from Step A of Example 26 in 10 mL of 1,2-dichloromethane at room temperature was added 0.35 g of N-tBOC-O-benzyl-D-serine, 0.195 g of HOBT, and 0.30 g of EDC and stirred for 18h. The reaction mictured was poured into 10mL of water and extracted with $CH_2Cl_2$ (2X10 mL). The combined organics were washed with 20 mL of 10% citric acid, 20 mL of saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated.

**[0102]** To a solution of the intermediate obtained from Step A in 5 mL of $CH_2Cl_2$ was added 5 mL of trifluoroacetic acid and stirred at RT for 30 min. The reaction mixture was concentrated, diluted with 5.0 mL of dichloromethane and carefully basified with 10 mL of 10% aqueous sodium carbonate solution. The organic layer was separated and the aqueous layer was further extracted with 2X15 mL of dichloromethane. The combined organics were washed with 5 mL of water, dried over potassium carbonate, filtered and concentrated to give 0.39 g of the amine as a thick oil.

**[0103]** To 0.39 g of the above intermediate in 10 mL of 1,2-dichloromethane at room temperature was added 0.24 g of N-tBOC-α-methylalanine, 0.195 g of HOBT, and 0.30 g of EDC and stirred for 18h. The reaction mixtured was poured into 10 mL of water and extracted with $CH_2Cl_2$ (2X10 mL). The combined organics were washed with 20 mL of 10% citric acid, 20 mL of saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. Flash chromatography of the residue over 30 g of silica gel with hexane-ethyl acetate (2:1) as eluent gave 0.33 g of product

$^1H$ NMR (200MHz, $CDCl_3$) δ 7.80(bs, 1H), 7.50-7.15 (m, 5H), 7.10(bd, 1H), 6.90-6.70(m, 1H), 6.27 (bd, 1H), 7.35-7.10 (m, 5H), 5.35-5.10 (m, 3H), 4.99 (s, 1H), 4.70-4.40 (m, 3H), 3.90-3.50 (m, 4H), 3.15-2.90 (m, 2H), 2.80-2.50 (m, 2H), 1.80-1.40 (m, 2H), 1.50 (3H), 1.42 (s, 6H).

Step B: N-[1(R)-[(1,2-Dihydro-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl] -[[(1,1-dimethylethyloxy)carbonyl]aminol-2-methylpropanamide

**[0104]** To a solution of 0.330 g of the intermediate obtained from Step A in 5 mL of ethanol at was added 1 drop of triethylamine and hydrogenated with hydrogen balloon for 3h. The catalyst was filtered off through a pad of celite and washed with ethyl acetate. The filtrate was concentrated to give 0.269 g of the product as a colorless foam.
$^1$H NMR (400MHz, $CDCl_3$) δ 7.35-7.20 (m, 4H), 7.17-7.08 (m, 2H), 6.80-6.65 (m, 2/2/3H), 6.27 (dt, 1/3H), 5.20-5.10 (m, 1H), 4.90 (s, 1H), 4.60-4.40 (m, 3H), 4.00 (bt, 1H), 3.75-3.60 (m, 1H), 3.55-3.40 (m, 3H), 3.18-3.30 (m, 2H), 2.90-2.65 (m, 1H), 1.83-1.50 (m, 4H), 1.48 (s, 4H), 1.42 (s, 2H), 1.39 (s, 9H).

Step C: N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl] -[[(1,1-dimethylethyloxy)carbonyl]-amino]-2-methylpropanamide

**[0105]** To a solution of 0.134 g the intermediate from Step B in 5 mL of dichloromethane was added 0.080 mL of N-methylmorpholine, and 0.022 mL of methanesulfonylchloride and stirred at 0°C for 30 min. The reaction mixture was diluted with an additional 5 mL of dichloromethane and washed with 5 mL of saturated sodium bicarbonate solution, brine (5 mL), dried over MgSO4 and concentrated. Flash chromatography of the residue over 20 g of silica gel gave 0.101 g of the desired product.
$^1$H NMR (400MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 7.08 (d, 1H), 6.95-6.80 (m, 2/1/3H), 6.23 (dd, 2/3H), 5.20-5.10 (m, 1H), 4.90 (bs, 1H), 4.60 (bd, 2/3H), 4.58-4.40 (m, 3/1/3H), 4.10-4.00 (m, 1H), 3.388-3.70 (m, 21/3H), 3.66-3.60 (m, 1/2H), 3.60-3.50 (m, 1H), 3.10-2.95 (m, 1H), 2.86 (s, 1H), 2.84 (s, 2H), 2.80 (t, 1/3H), 2.65 (t, 2/3H), 2.90-2.50 (m, 4H), 1.45 (s, 4H), 1.44 (s, 2H), 1.42 (s, 3H), 1.40 (s, 6H).

Step D: N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

**[0106]** To a solution of 0.101 g the intermediate from Step C in 1mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and maintained at RT for 30 min. The reaction mixture was evaporated to dryness, basified with 10% aqueous sodium carbonate solution (10 mL), and extracted with dichloromethane (3X5 mL). The combined organics were washed with brine (5 mL), dried over potassium carbonate, and concentrated. This material was dissolved in 2 mL of ethyl acetate and 0.10 mL of 4M HCl in EtOAc was added at 0°C. The precipitate was filtered under nitogen and washed with EtOAc/ether (1:1) and dried to give 62 mg of the product as a white solid.
1H NMR (400MHz, $CD_3OD$) δ 7.40-7.20 (m, 5H), 7.08 (d,1H), 6.95-6.80 (m, 2/1/3H), 6.23 (dd, 2/3H), 5.20-5.10 (m, 1H), 4.60 (bd, 2/3H), 4.58-4.40 (m, 3/1/3H), 4.10-4.00 (m, 1H), 3.388-3.70 (m, 21/3H), 3.66-3.60 (m, 1/2H), 3.60-3.50 (m, 1H), 3.10-2.95 (m, 1H), 2.86 (s, 1H), 2.84 (s, 2H), 2.80 (t, 1/3H), 2.65 (t, 2/3H), 2.90-2.50 (m, 4H), 1.45 (s, 4H), 1.44 (s, 2H).

EXAMPLE 29

Step A: N-[1(R)-[(1,2-Dihydro-1-benzenesulfonyl-5-fluoro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

**[0107]** To a solution of 0.026 g the intermediate from Step B of Example 27 in 2 mL of dichloromethane was added 0.020 mL of N-methylmorpholine, and 0.012 mL of benzeneesulfonylchloride and stirred at 0°C for 1h. The reaction mixture was poured into 10 mL of ether and washed with 5 mL of saturated sodium bicarbonate solution, dried over $MgSO_4$ and concentrated. Flash chromatography of the residue over 10 g of silica gel with $CH_2Cl_2$-ether (2:1) as eluent gave 0.019 g of the product.

**[0108]** This material was treated with 1 mL of dichloromethane and 1 mL of trifluoroacetic acid for 1h. The reaction mixture was evaporated to dryness and the residue was triturated with ether to give 18 mg of the desired product as a white solid.
$^1$H NMR (400MHz, $CD_3OD$) δ 7.80 (d, 2H), 7.70-7.55 (m, 2H), 7.55-7.50 (m, 2H), 7.40-7.20 (m, 42/3H), 7.03-6.92 (m, 1H), 6.82 (dt, 2/3H), 6.47 (dt, 2/3H), 5.08 (dt, 1H), 4.60-4.48 (m, 2H), 4.33 (bt, 1H), 3.94-3.85 (m, 3H), 3.75-3.65 (m, 2H), 3.10 (dt, 1H), 2.80 (dt, 1H), 1.73 (dt, 1H), 1.58 (s, 4H), 1.56 (s, 2H), 1.50 (dt, 1H), 1.38 (dt, 1H), 1.10 (dt, 2H).

EXAMPLE 30

N-[1(R)-[(1,2-Dihydro-1-ethanesulfonyl-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

Step A: N-[1(R)-[(1,2-Dihydro-1-benzyloxycarbonyl-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)-ethyl]-[[(1,1-dimethylethyloxy)carbonyl]amino]-2-methylpropanamide

**[0109]** To 5 g of the 1,2-Dihydro-1-benzyloxycarbonyl-spiro[3H-indole-3,4'-piperdine] hydrochloride in 100 mL of dichloromethane at room temperature was added 3.64 g of N-tBOC-O-benzyl-D-serine, 1.83 g of HOBT, 2.60 mL of N-methylmorpholine, and 3.70 g of EDC and stirred for 18h. The reaction mixture was poured into 100 mL of water and extracted with $CH_2Cl_2$ (2X100 mL). The combined organics were washed with 100 mL of 10% citric acid, 100 mL of saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated.

**[0110]** To a solution of the intermediate obtained from Step A in 20 mL of $CH_2Cl_2$ was added 20 mL of trifluoroacetic acid and stirred at RT for 30 min. The reaction mixture was concentrated, diluted with 50 mL of dichloromethane and carefully basified with 100 mL of 10% aqueous sodium carbonate solution. The organic layer was separated and the aqueous layer was further extracted with 2X50 mL of dichloromethane. The combined organics were washed with 50 mL of water, dried over potassium carbonate, filtered and concentrated to give the amine as a thick oil.

**[0111]** To the above intermediate in 50 mL of dichloromethane at room temperature was added 2.50 g of N-tBOC-α-methylalanine, 1.83 g of HOBT, and 3.70 g of EDC and stirred for 18h. The reaction mixtured was poured into 10 mL of water and extracted with $CH_2Cl_2$ (2X10 mL). The combined organics were washed with 20 mL of 10% citric acid, 20 mL of saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. Flash chromatography of the residue over 300g of silica gel with hexane-ethyl acetate (2:1) as eluent gave 8.1 g of product

$^1$H NMR (400MHz, $CDCl_3$) δ 7.85(bs, 1H), 7.45-7.20 (m, 10H), 7.20-7.05 (m, 22/3H), 6.95 (t, 1/3H), 6.88(t, 1/3H), 6.53 (dd, 2/3H), 5.35-5.20 (m, 2H), 5.20-5.10 (m, 1H), 4.92 (bs, 1H), 4.65-4.20 (m, 4H), 4.05 (bd, 2/3H), 4.00-3.80 (m, 1,1/3H), 3.80-3.60 (m, 1H), 3.10 (t, 2/3H), 3.00-2.85 (m, 1/3H), 2.82-2.60 (2t, 1H), 1.90-1.55 (m, 5H), 1.49 (s, 4H), 1.42 (s, 2H), 1.40 (s, 9H).

Step B: N-[1(R)-[(1,2-Dihydro-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl] -[[(1,1-dimethylethoxy)carbonyl]amino]-2-methylpropanamide

**[0112]** To a solution of 8.10 g of the intermediate obtained from Step A in 80 mL of ethanol was added 1 g of 20% palladium hydroxide/C and hydrogenated with hydrogen balloon for 1h. The catalyst was filtered off through a pad of celite and washed with ethyl acetate. The filtrate was concentrated to give 4.69 g of the product as a colorless foam.

$^1$H NMR (400MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H), 7.18 (d, 1/2H), 7.10 (d, 1/2H), 7.04-6.98 (m, 2H), 6.75-6.60 (m, 2H), 5.20-5.10 (m, 1H), 4.97 (bs, 1H), 4.55-4.40 (m, 3H), 3.95 (dd, 1H), 3.73-3.61 (m, 1H), 3.60-3.50 (m, 1H), 3.50-3.33 (m, 3H), 3.10 (dt, 1H), 2.83 (dt, 1H), 1.85-1.55 9m, 5H), 1.47 (s, 4H), 1.42 (s, 2H), 1.39 (s, 9H).

Step C: N-[1(R)-[(1,2-Dihydro-1-ethanesulfonyl-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)-ethyl]-2-amino-2-methylpropanamide

**[0113]** To a solution of 0.158 g the intermediate from Step B in 5 mL of dichloromethane was added 0.053 mL of N-methylmorpholine, and 0.034 mL of ethanesulfonylchloride and stirred at 0°C for 30 min and RT for 1h. The reaction mixture was diluted with an additional 5 mL of dichloromethane and washed with 5 mL of saturated sodium bicarbonate solution, brine (5 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the residue over 10 g of silica gel with $CH_2Cl_2$-ether (3:1) as eluent gave 0.057 g of the desired product.

**[0114]** To a solution of 0.057 g the above intermediate in 1 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and maintained at RT for 30 min. The reaction mixture was concentrated to dryness and triturated with ether to give 0.034 g of the product as a yellow solid.

$^1$H NMR (400MHz, $CD_3OD$) δ 7.40-7.25(m, 5H), 7.25-7.13 (m, 21/2H), 7.03 (t, 1/2H), 6.95 (t, 1/2H), 6.80 (d, 1/2H), 5.18 (dt, 1H), 4.60-4.42 (m, 3H), 4.08 (t, 1H), 3.96 (s, 2H), 3.83-3.70 (m, 2H), 3.29-3.15 (m, 3H), 2.84 (dt, 1H), 1.90 (dt, 1H), 1.74-1.62 (m, 4H), 1.62 (s, 2H), 1.60 (s, 4H), 1.33 (dt, 3H).

EXAMPLE 31

Step A: N-[1(R)-[(1,2-Dihydro-1-[2-methyl-2-propanesulfonyl-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-[[(1,1-dimethylethyloxy)-carbonyl]amino]-2-methylpropanamide

**[0115]** To a solution of 0.212 g the intermediate from Step B of Example 29 in 2 mL of 1,2-dichloroethane was added 0.083 mL of triethylamine, and 0.054 mL of isopropylsulfonylchloride and stirred at 0°C for 30 min and at RT for 3h. The reaction mixture was diluted with a 5 mL of dichloromethane and washed with 5 mL of saturated sodium bicarbonate solution, brine (5 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the residue over 10 g of silica gel with $CH_2Cl_2$-ether (3:1) as eluent gave 0.113 g of the desired product.

**[0116]** To a solution of 0.101 g the above intermediate in 1 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and maintained at RT for 30 min. The reaction mixture was evaporated to dryness, basified with 10% aqueous sodium carbonate solution (10 mL), and extracted with dichloromethane (3X5 mL). The combined organics were washed with brine (5 mL), dried over potassium carbonate, and concentrated. This material was dissolved in 2 mL of ethyl acetate and 0.10 mL of 4M HCl in EtOAc was added at 0°C. The precipitate was filtered under nitogen and washed with EtOAc/ether (1:1) and dried to give 88 mg of the product as a white solid.

$^1$H NMR (400MHz, $CD_3OD$) δ 7.40-7.20 (m, 5H), 7.08 (d,1H), 6.95-6.80 (m, 2/1/3H), 6.23 (dd, 2/3H), 5.20-5.10 (m, 1H), 4.60 (bd, 2/3H), 4.58-4.40 (m, 3/1/3H), 4.10-4.00 (m, 1H), 3.388-3.70 (m, 21/3H), 3.66-3.60 (m, 1/2H), 3.60-3.50 (m, 1H), 3.10-2.95 (m, 1H), 2.86 (s, 1H), 2.84 (s, 2H), 2.80 (t, 1/3H), 2.65 (t, 2/3H), 2.90-2.50 (m, 4H), 1.45 (s, 4H), 1.44 (s, 2H).

EXAMPLE 32

Step A: N-[1(R)-[(1,2-Dihydro-1-[2-carbomethoxymethanesulfonyl-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-[[(1,1-dimethylethyloxy)-carbonyl]-amino]-2-methylpropanamide hydrochloride

**[0117]** To a solution of 0.50 g the intermediate from Step B of Example 29 in 10 mL of dichloromethane was added 0.21 mL of N-methylmorpholine and 0.10 mL of 2-carbomethoxymethanesulfonylchloride and stirred at 0°C for 30 min. The reaction mixture was diluted with 10 mL of dichloromethane and washed with 5 mL of saturated sodium bicarbonate solution, brine (5 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the residue over 20 g of silica gel with $CH_2Cl_2$-ether (3:1) as eluent gave 0.529 g of the desired product.

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.39-7.20 (m, 5H), 7.20-7.10 (m, 21/2H), 7.08 (dt, 1H), 6.92 (t, 1/2H), 6.55 (d, 1/2H), 5.20-5.10 (m, 1H), 4.94 (bs, 1H), 4.60 (bd, 1H), 4.53-4.40 (m, 2H), 4.10 (2bs, 2H), 4.05-3.90 (m, 2H), 3.70 (dt, 1H), 3.63 (s, 11/2H), 3.61 (s, 11/2H), 3.59-3.50 (m, 1H), 3.05 (dt, 1H), 2.70 (dt, 1H0, 1.90-1.50 (m, 4H), 1.49 (s, 4H), 1.44 (s, 2H), 1.39 (s, 9H).

Step B: N-[1(R)-[(1,2-Dihydro-1-[2-carbomethoxymethanesulfonyl-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

**[0118]** To a solution of 0.113 g the above intermediate in 1 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and maintained at RT for 30 min. The reaction mixture was evaporated to dryness, basified with 10% aqueous sodium carbonate solution (10 mL), and extracted with dichloromethane (3X5 mL). The combined organics were washed with brine (10 mL), dried over potassium carbonate, and concentrated. This material was dissolved in 2 mL of ethyl acetate and 0.20 mL of 4M HCl in EtOAc was added at 0°C. Ether was added and the precipitate was filtered under nitogen and washed with ether and dried to give 0.108 g of the product as a white solid.

$^1$H NMR (400MHz, $CD_3OD$) δ 7.40-7.20 (m, 5H), 7.08 (d,1H), 6.95-6.80 (m, 2/1/3H), 6.23 (dd, 2/3H), 5.20-5.10 (m, 1H), 4.60 (bd, 2/3H), 4.58-4.40 (m, 3/1/3H), 4.10-4.00 (m, 1H), 3.388-3.70 (m, 21/3H), 3.66-3.60 (m, 1/2H), 3.60-3.50 (m, 1H), 3.10-2.95 (m, 1H), 2.86 (s, 1H), 2.84 (s, 2H), 2.80 (t, 1/3H), 2.65 (t, 2/3H), 2.90-2.50 (m, 4H), 1.45 (s, 4H), 1.44 (s, 2H).

EXAMPLE 33

Step A: N-[1(R)-[(1,2-Dihydro-1-[2-carboxymethanesulfonyl-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-[[(1,1-dimethylethyloxy)-carbonyl]amino]-2-methylpropanamide trifluoroacetate

**[0119]** To a solution of 0.126 g the intermediate from Step A of Example 32 in 3 mL of methanol and 1 mL of water at 0°C was added 2 drops of 5N aqueous sodium hydroxide and stirred for 30 min. The reaction mixture was acidified to pH=2 with 0.50N aqueous hydrochloric acid, diluted with brine (5 mL), and extracted with $CH_2Cl_2$ (2X5 mL). The

combined organics were washed with brine(10 mL), dried over $MgSO_4$ and concentrated to give 0.098 g of a white foam. $^1H$ NMR (400MHz, $CDCl_3$) δ 9.80 (bs, 1H), 7.45 (d, 1/2H), 7.40-7.13 (m, 7H), 7.02 (t, 1/2H), 6.90 (t, 1/2H), 6.50 (d, 1/2H), 5.22-5.10 (m, 1H), 4.60-4.40 (m, 3H), 4.20-4.00 (m,3H), 3.92 (d, 1H), 3.70-5.50 (m, 2H), 3.04 (dt, 1H), 2.70 (dt, 1H), 1.93-1.50 (m, 4H), 1.42 (s, 6H), 1.33 (s, 9H).

Step B: N-[1(R)-[(1,2-Dihydro-1-[2-carboxymethanesulfonyl-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide

**[0120]** To a solution of 0.098 g the intermediate from Step A in 1 mL of dichloromethane was added 1 mL of trifluoroacetic acid and stirred for 30 min. The reaction mixture was evaporated to dryness and triturated with ether to 0.096 g of the product as a white solid.
$^1H$ NMR (400MHz, $CD_3OD$) δ 7.40-7.28 (m, 6H), 7.24-7.15 (m, 21/2H), 7.00 (dt, 1H), 6.80 (d, 1/2H), 5.17 (dt, 1H), 4.60-4.45 (m, 2H), 4.22 (d, 2H), 4.14-4.00 (m, 3H), 3.81-3.70 (m, 2H), 3.22 (dt, 1H), 2.83 (dt, 1H), 1.96 (dt, 1/2H), 1.80-1.64 (m, 41/2H), 1.62 (s, 1H), 1.60 (s, 5H).

EXAMPLE 34

Step A: N-[1(R)-[(1,2-Dihydro-1-[2-hydroxyethanesulfonyl-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-[[(1,1-dimethylethyloxy)-carbonyl]amino]-2-methylpropanamide trifluoroacetate

**[0121]** To a solution of 0.222 g the intermediate from Step A of Example 32 in 2 mL of 2 mL of anhydrous tetrahydrofuran at RT was added was added 0.48 mL of 2M solution of lithium borohydride in tetrahydrofuran and stirred for 3h. The reaction mixture was quenched with 0.50 mL of acetone, diluted with 15 mL of water and extracted with $CH_2Cl_2$ (2X15 mL). The combined organics were washed with brine(10 mL), dried over $MgSO_4$ and concentrated to give 0.27 g of a white foam. Flash chromatography of the residue over 10g of silica gel with $CH_2Cl_2$-acetone (2:1) as eluent gave 0.129 g of the desired material as a thick oil.
$^1H$ NMR (400MHz, $CDCl_3$) δ 7.32-7.20 (m, 6H), 7.20-7.10 (m, 2H), 7.09 (d, 1/2H), 6.98 (t, 1/2H), 6.90 (t, 1/2H), 6.54 (d, 1/2H), 5.17-5.10 (m, 1H), 5.00 (bs, 1H), 4.61-4.39 (m, 3H), 4.10-3.95 (m, 5H), 3.93-3.74 (m, 2H), 3.66 (ddd, 1H), 3.53 (dt, 1H), 3.27 (dt, 2H), 3.00 (dt, 1H), 2.70 (dt, 1H), 1.90-1.50 (m, 4H), 1.43 (s, 4H), 1.41 (s, 2H), 1.36 (s, 9H).

Step B: N-[1(R)-[(1,2-Dihydro-1-[2-hydroxyethanesulfonyl-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(phenylmethoxy)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

**[0122]** To a solution of 0.129 g the intermediate from Step A in 1mL of dichloromethane was added 1 mL of trifluoroacetic acid and stirred for 30 min. The reaction mixture was evaporated to dryness and triturated with ether to 0.113 g of the product as a white solid.
$^1H$ NMR (400MHz, $CD_3OD$) δ 7.40-7.25 (m, 6H), 7.25-7.13 (m, 21/2H), 6.98 (dt, 1H), 6.80 (d, 1/2H), 5.20-5.10 (m, 1H), 4.60-4.43 (m, 3H), 4.10-3.90 (m, 5H), 3.81-3.70 (m, 2H), 3.40-3.33 (dt, 2H), 3.20 (dt, 1H), 3.82 (dt, 1H), 2.00-1.63 (m, 4H), 1.61 (s, 1H), 1.58 (s, 5H).

EXAMPLE 35

Step A: N-[1(R)-[(1,2-Dihydro-1-trifluoromethanemethanesulfonyl-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-[[(1,1-dimethylethyloxy)-carbonyl]amino]-2-methylpropanamide hydrochloride

**[0123]** To a solution of 0.150 g the intermediate from Step B of Example 29 in 5 mL of dichloromethane was added 0.10 mL of N-methylmorpholine and 0.057 mL of trifluoromethanesulfonic anhydride and stirred at 0°C for 15 min. The reaction mixture was diluted with 5 mL of saturated aqueous sodium bicarbonate solution and extracted with 2X5 mL of dichloromethane. The combined organics were washed with brine (5 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the residue over 10 g of silica gel with hexane-acetone (3:1) as eluent gave 0.136 g of the desired product.
$^1H$ NMR (400 MHz, $CDCl_3$) δ 7.40-7.15 (m, 6H), 7.15-6.93 (m, 21/2H), 6.53 (d, 1/2H), 5.20-5.10 (m, 1H), 4.90 (bs, 1H), 4.70-4.60 (m, 3H), 4.15-3.90 (m, 3H), 3.70 (ddd, 1H), 3.60-3.50 (m, 1H), 3.00 (dt, 1H), 2.70 (dt, 1H), 1.93-1.55 (m, 4H), 1.46 (s, 4H), 1.43 (s, 2H), 1.40 (s, 9H).

Step B: N-[1(R)-[(1,2-Dihydro-1-trifluoromethanesulfonyl-spiro[3H-indole-3,4'-piperdin]]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

**[0124]** To a solution of 0.136 g the above intermediate in 1 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and maintained at RT for 30 min. The reaction mixture was evaporated to dryness, basified with 10% aqueous sodium carbonate solution (5 mL), and extracted with ethylacetate (2X5 mL). The combined organics were washed with brine (5 mL), dried over potassium carbonate, and concentrated. This material was dissolved in 2 mL of ethyl acetate and 0.20 mL of 4M HCl in EtOAc was added at 0°C. Ether was added and the precipitate was filtered under nitrogen and washed with ether and dried to give 0.94 g of the product as a white solid.
$^1$H NMR (400 MHz, $CD_3OD$) δ 7.40-7.15 (m, 6H), 7.15-6.93 (m, 21/2H), 6.53 (d, 1/2H), 5.20-5.10 (m, 1H), 4.90 (bs, 1H), 4.70-4.60 (m, 3H), 4.15-3.90 (m, 3H), 3.70 (ddd, 1H), 3.60-3.50 (m, 1H), 3.00 (dt, 1H), 2.70 (dt, 1H), 1.93-1.55 (m, 4H), 1.46 (s, 4H), 1.43 (s, 2H).

EXAMPLE 36

Step A: N-[1(R)-[(1,2-Dihydro-1-benzenesulfonyl-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

**[0125]** To a solution of 0.148 g the intermediate from Step B of Example 29 in 3 mL of dichloromethane was added 0.30 mL of N-methylmorpholine and 0.022 mL of benzenesulfonyl chloride and stirred at room temperature for 1h. The reaction mixture was diluted with 10 mL of dichloromethane and washed with 10 mL of saturated aqueous sodium bicarbonate solution, dried over $MgSO_4$ and concentrated. Flash chromatography of the residue over 10 g of silica gel with hexane-acetone (3:1) as eluent gave 0.190 g of the desired product.
**[0126]** To a solution of 0.190 g the above intermediate in 3 mL of dichloromethane was added 3 mL of trifluoroacetic acid and maintained at RT for 30 min. The reaction mixture was evaporated to dryness, basified with 10% aqueous sodium carbonate solution (5 mL), and extracted with ethylacetate (2X5 mL). The combined organics were washed with brine (5 mL), dried over potassium carbonate, and concentrated. This material was dissolved in 2 mL of ethyl acetate and 0.40 mL of 4M HCl in EtOAc was added at 0°C. Ether was added and the precipitate was filtered under nitogen and washed with ether and dried to give 0.136 g of the product as a white solid.
$^1$H NMR (400MHz, $CD_3OD$) δ 7.82 (d, 2H), 7.67-7.58 (m, 2H), 7.52 (t, 2H), 7.40-7.20 (m, 6H), 7.10-6.90 (m, 11/2H), 6.68 (d, 1/2H), 5.10 (dt, 1H), 4.53 (ABq, 2H), 4.35 (t, 1H), 4.00-3.80 (m, 3H), 3.75-3.65 (m, 2H), 3.10 (dt, 1H), 2,73 (dt, 1H), 1.75 (dt, 1/2H), 1.48 (m, 11/2H), 1.20-1.05 (m, 2H).

EXAMPLE 38

N-[1(R)-[(1,2-Dihydro-1-[1-methoxycarbonyl-1-methyl-ethanesulfonyl-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

Step A: 1,2-Dihydro-1-[1-methoxycarbonyl-1-methyl-ethanesulfonyl]-spiro[3H-indole-3,4'-piperdine]

**[0127]** To 5.06 g of 1,2-Dihydro-1-benzyloxycarbonyl-spiro[3H-indole-3,4'-piperdine] hydrochloride in 50 mL of dichloromethane was added 3.0 mL of triethylamine and 3.40 g of di-t-butylcarbonate and stirred at room temperature for 3h. The reaction mixture evaporated to dryness and diluted with 100 mL of ether and washed with 50 mL of 0.50N aqueous hydrochloric acid, 50 mL of brine, dried over $MgSO_4$ and concentrated. To this crude product in 50 mL of ethanol was added 1g of 20% palladium hydroxide on carbon and hydrogenated with H2 balloon overnight. To 0.506 g of this compound in 15 mL of dichloromethane at 0°C was added 0.74 mL of triethylamine and 0.41 mL of carbomethoxymethanesulfonyl chloride and stirred for 1h. The reaction mixture was diluted with 25 mL of ether and washed with saturated sodium bicarbonate solution (20 mL), dried over $MgSO_4$, and concentrated. Flash chromatography of the residue over 25 g of silica gel with hexane-ethyl acetate 4:1 as eluent gave 1.79 g of the desired material as a thick oil.
**[0128]** Sodium hydride (0.102 g of 60% in mineral oil) was washed with hexanes and then suspended in 5 mL of dry DMF. A solution of 0.158 g of the above intermediate in 1 mL of DMF was added and stirred for 30 min. Methyl iodide (1.85 mmol) was added and stirred for 3h. The reaction mixture was poured into 15 mL of saturated aqueous ammonium chloride solution and extracted with ether (2X15 mL). The combined organics were washed with water (15 mL), brine (15 mL), dried over $MgSO_4$ and concentrated to give 0.179 g of the desired material.
$^1$H NMR (200 MHz, $CDCl_3$) δ 7.32 (d, 1H), 7.20-6.90 (m, 3H), 4.13 (bd, 2H), 2.83 (bt, 2H), 1.85-1.70 (m, 4H), 1.69 (s, 6H), 148 (s, 9H).

Step B: N-[1(R)-[(1,2-Dihydro-[1-methoxycarbonyl-1-methylethanesulfonyl]-spiro[3H-indole-3,4'-piperdin]-1'-yl) carbonyl]-2-(indol-3-yl)ethyl]-[[(1,1-dimethylethyloxy)-carbonyl]amino]-2-methylpropanamide

**[0129]** To a solution of 0.179 g of the intermediate from Step A was added 1 mL of dichloromethane and 1 mL of trifluoroacetic acid and stirred for 30 min. The reaction mixture was evaporated to dryness, basified with 10 mL of 10% aqueous sodium carbonate solution and extracted with 2X10 mL of dichloromethane. The combined organics were washed with brine (10 mL), dried over potassium carbonate, filtered, and concentrated to 0.120 g of the piperidine as a thick oil. To a solution of this compound in 5 mL of dichloromethane was added 0.132 g of the acid intermediate prepared in Example 21 Step B, 0.055 g of HOBT, 0.102 g of EDC and stirred for 18h. The reaction mixture was diluted with 25 mL of ether and washed with 15 mL of 0.05N HCl, saturated sodium bicarbonate solution (15 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the residue over 20 g of silica gel with $CH_2Cl_2$-acetone (5:1) as eluent gave 0.094 g of the desired product.
$^1H$ NMR ($CDCl_3$, 400MHz) δ 8.60 (s, 2/3H), 8.50 (s, 1/3H), 7.70 (d, 2/3H), 7.60 (d, 1/3H), 7.35 (d, 2/3H), 7.30 (d, 1/3H), 7.26-7.00 (m, 5H), 6.90 (t, 11/3H), 6.40 (d, 2/3H), 5.28-5.16 (m, 1H), 5.05 (bs, 1H), 4.41 (bd, 2/3H), 4.32 (bd, 1/3H), 3.78-3.65 (m, 2H), 3.56 (s, 2H), 3.55 (s, 1H), 3.50 (bd, 1H), 3.20 (dt, 1H), 3.15 (ddd, 1H), 2.75 (t, 1H), 2.42 (m, 1H), 1.18 (d, 2H), 1.24 (s, 4H), 1.50 (s, 2H), 1.48 (s, 4H), 1.42 (s, 9H), 1.30-1.18 (m, 1H), 1.10-0.90 (m, 11/3H), 0.03 (dt, 2/3H).

Step C: N-[1(R)-[(1,2-Dihydro-[1-methoxycarbonyl-1-methylethanesulfonyl]-spiro[3H-indole-3,4'-piperdin]-1'-yl) carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide trifluoroacetate

**[0130]** A solution of 0.094 g of the intermediate from Step C was treated with 1 mL of dichloromethane and 1 mL of trifluoroacetic acid for 30 min., evaporated to dryness and triturated with ether to give 0.082 g of the desired product.
$^1H$ NMR ($CD_3OD$, 400MHz) δ 7.70 (d, 2/3H), 7.60 (d, 1/3H), 7.35 (d, 2/3H), 7.30 (d, 1/3H), 7.26-7.00 (m, 5H), 6.90 (t, 11/3H), 6.40 (d, 2/3H), 5.28-5.16 (m, 1H), 5.05 (bs, 1H), 4.41 (bd, 2/3H), 4.32 (bd, 1/3H), 3.78-3.65 (m, 2H), 3.56 (s, 2H), 3.55 (s, 1H), 3.50 (bd, 1H), 3.20 (dt, 1H), 3.15 (ddd, 1H), 2.75 (t, 1H), 2.42 (m, 1H), 1.18 (d, 2H), 1.24 (s, 4H), 1.50 (s, 2H), 1.48 (s, 4H), 1.30-1.18 (m, 1H), 1.10-0.90 (m, 11/3H), 0.03 (dt, 2/3H).

EXAMPLE 43

N-[1(R)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-4-phenylbutyl]-2-amino-2-methylpropanamide hydrochloride

Step A: N-[1(R)-[1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'yl)carbonyl]-4-phenylbutyl]-2-amino-2-methylpropanamide hydrochloride

**[0131]** This compound was prepared from 2(R)-N-t-butoxycarbonyl-5-phenylpetanoic and 1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdine] hydrochloride using chemistry described for the preparation of compound in Example 18.
FAB MS Calc. for $C_{28}H_{38}N_4O_4S$:MW = 526.2; found m/e = (m+1) 527.9

EXAMPLE 50

N-[1(R)-[spiro[benzo[b]thiophene-3(2H),4'-piperidine]-1'-yl carbonyl-2-indole-3-yl )ethyl-2-amino-2-methylpropanamide hydrochloride

Step A: 1-[(1,1-dimethylethoxy)carbonyl]-3-hydroxy-4-methylene-1,2,5,6-tetrahydropyridine

**[0132]** To a suspension/solution of methyltriphenylphosphonium iodide (30 g, 74 mmole) in 150 mL of THF was slowly added butyllithium (2.5 N, 25.5 mL, 63.7 mmole) at 0°C. After stirring an hour at room temperature, N-t-BOC protected 4-piperidone (prepared from 4-piperidone monohydrate hydrochloride by the procedure described in Protective Groups in Organic Synthesis T. W. Greene, John Wiley and Sons, NY. 1981.) in 50 mL of THF was added to reaction mixture at room temperature slowly. This reaction was stirred for 2 hours and filtered. The filtrate was concentrated and purified (MPLC, silica gel, hexanes/ethyl acetate=10/1) to give the Wittig product (7.9 g) in 82% yield.
**[0133]** To a suspension of selenium dioxide/silica gel (prepared according to the procedure described in *Chem. lett.* **1981**, 1703) in 30 mL methylene chloride was added t-butyl hydroperoxide (1.23 mL). After 15 minutes, the Wittig product (0.72 g, 3.69 mmole) in 5 mL of methylene chloride was added. The cloudy solution was stirred for 3 hours and filtered though Celite. The filtrate was washed with water, brine and dried over sodium sulfate. The organic layer was concentrated and purified by flash chromatography (hexanes/ethyl acetate=4/1) to give the title compound in 52%

yield (0.41 g).

Step B: 1-[(1,1-dimethylethoxy)carbonyl]-4-chloromethyl-1,2,5,6-tetrahydropyridine

**[0134]** The intermediate obtained from Step A (400 mg, 1.88 mmole) was dissolved in 10 mL benzene and thionyl chloride (165 ml, 2.26 mmole) was added and heated to 60°C for 25 minutes. The resulting mixture was poured into $NaHCO_3$ (aq.) and extracted with ether. The ether layer was dried over magnesium sulfate and concentrated to give title compound (333 mg, 77%).

Step C: 1-[(1,1-dimethylethoxy)carbonyl]-4-[[(2-bromophenyl)-thio]methyl-1,2,5,6-tetrahydropyridine

**[0135]** The intermediate obtained from Step B (330 mg, 1.43 mmole) was dissolved in 10 mL of acetone and 2-bromothiophenol (172 ml, 1.43 mmole) and potassium carbonate (390 mg, 2.86 mmole) were added. The reaction mixture was heated to 60°C for an hour and then filtered though silica gel (100% ether). The organic layer was concentrated and purified by flash chromatography (silica gel, hexanes/ethyl acetate=10/1) to give the title compound in 84% yield (460 mg).

Step D: 1'-[(1,1-dimethylethoxy)carbonyl]-spiro[benzo[b]thiophene-3-(2H),y'-piperdine

**[0136]** The intermediate obtained from Step C (450 mg, 1.17 mmole) was dissolved in 60 mL of benzene and AIBN (10 mg) and tributyltin hydride (644 mL, 2.39 mmole) were added. This mixture was refluxed for 2 hours and concentrated. The residue was dissolved in ether and bromine was added till the reaction solution turned to a brownish color. To this brownish solution at room temperature was added DBU (650 mL) in dropwise manner. The resulting cloudy solution was filtered though silical gel and washed with ether. The ether solution was concentrated and the residue was purified by radial chromatography (silic gel, hexanes/ethyl acetate=10/1) to give title compound (157 mg) in 43% yield.

Step E: N-[1(1R)-[spiro[benzo[b]thiophene-3(2H), y'-piperdine]-1'-yl)carbonyl]-2-(indole-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride

**[0137]** A solution of the intermediate obtained from Step D (50 mg, 0.164 mmole) in 0.5 mL of TFA was stirred at room temperature for 1/2 hour and then concentrated. The residue was diluted with chloroform and washed with $NaHCO_3$ (aq.). The organic layer was dried over sodium sulfate, filtered and concentrated to give free amine (32 mg) in 95%. A solution of free amine (5.1 mg, 0.025 mmole) in 1 ml chloroform was added the intermediate obtained from Example 21 Step C (9.2 mg, 0.0246 mmole), HOBt (4.0 mg, 0.0295 mmole) and EDC (5.6 mg, 0.0295 mmole) at room temperature. After 12 hours, the reaction was poured into water and extracted with chloroform. The chloroform layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by Preparative -TLC (silica gel. hexanes/ethyl acetate=1/1) to give a colorless foam (13 mg, 94%). The title compound was obtained from this colorless foam according to the procedure described in Example 18, Step C.
$^1H$ NMR (400 MHz, $CD_3OD$) mixture of rotamers: δ 7.62 (d, 8 Hz, 2/3 H), 7.54 (d, 8 Hz, 1/3 H), 7.39 (d, 8 Hz, 2/3 H), 7.35 (d, 8 Hz, 1/3 H), 7.19-7.00 (m, 6 1/3 H), 2.62 (m, 1H), 1.72-1.65 (m, 2 1/3 H), 1.61 (s, 4H), 1.50 (s, 2H), 0.94 (m, 1H), 0.10 (m, 2/3 H). FAB-MS 477 (m+1).

EXAMPLE 52

N-[1(R)-[[1-[[[[6-[[[4-azido-2-hydroxy-5-iodophenyl]carbonyl]amino]-hexyl]amino]carbonyl]methyl]sulfonyl]-2,3-dihydrospiro[3H-indole-3,4'-piperidin]-1'-yl]carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2methylpropanamide hydrochloride

**[0138]** To a solution of the commercially available N-hydroxysuccimidyl-4-azido-2-hydroxy-benzoate in 5 mL of $CH_2Cl_2$ was added 6-N-t-butoxycarbonyl-n-hexylamine hydrochloride and 0.10 mL of Hunig's base and stirred for 4h. The reaction mixture was evaporated to dryness and chromatorgraphed on 15 g of silica gel. Elution with hexanes-ethyl acetate (2:1) gave 0.229 of the acylated product. To 29 mg of the above material was added 2 ml of THF and 2 mL of 0.01 M aqueous NaOH, 25 mg of potassium iodide. Chloramine-T (15 mg) was added and stirred for 30 min. The reaction was quenched with 2 mL of saturated sodium thiosulfate solution, diluted with 5 mL of 0.05N HCl and extracted with ethyl acetate (2X5 mL). The combined organics were washed with brine (5 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the residue (5 g silica gel) with hexane-ether (3:1) gave 26 mg of the iodonated material. Deprotection of the N-tBOC was carried out with 4M HCl in ethyl acetate to give 21.4 mg of the hydrochloride.

**[0139]** To solution of this material in 5 mL of $CH_2Cl_2$ was added 49 mg of the acid intermediate form Step A of Example 33, 0.016 mL of NMM, 19.8 mg of HOBT, and 29 mg of EDC and stirred for 18 h. The reaction was worked up and purified in the usual manner.

**[0140]** Once again deprotection of the N-tBOC group was carried with 4M HCl in ethyl acetate. This gave the title compound as a yellow-brown solid. This material was basified by dissolving in 2 mL of saturated $NaHCO_3$ and extracted with $CH_2Cl_2$ (2X3 mL). The combined organics were dried over $Na_2SO_4$ and concentrated to the title compound. $^1H$ NMR ($CDCl_3$, 400 MHz) The compound exists as a 3:2 mixture of rotamers. δ 8.40-8.20 (m, 1H), 7.95 (s, 2/3H), 7.90 (s, 1/3H), 7.40-6.90 (m, 9 1/3H), 6.70 (s, 2/3H), 6.55 (m, 1H), 5.20-5.10 (m, 1H), 4.70-4.40 (m, 4H), 4.10-3.80 (m, 5H), 3.80-3.50 (m, 4H), 3.40-3.10 (m, 4H), 3.10-3.00 (m,1H), 2.70 (dt, 1H), 1.90-1.20 (m, 14H), 1.30 (s, 6H).

EXAMPLE 55

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide mesylate

**[0141]** This compound was prepared by the treating the free base obtained in Example 18, Step C, with methane sulfonic acid. The title compound was obtained by recrystallizing it from ethyl acetate-ethanol-water. m.p. = 166°-168°C.

EXAMPLE 56

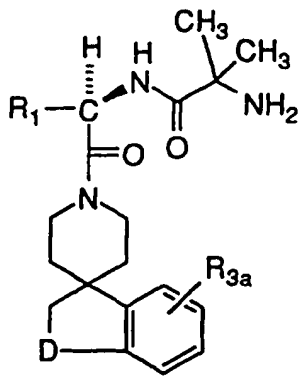
2,3,3a,4,6,6a-hexahydro-2-oxo-1H-thieno[3,4-d]imidazole-4(S)-pentanoic acid-6-[[[[[1'-[[(29R)-[[2-amino-2-methyl-1-oxopropyl]-amino]-3-(phenylmethyloxy)-1-oxopropyl]-2,3-dihydrospiro[3H-indole-3,4'-piperidin]-1'-yl]sulfonyl]methyl]carbonyl]amino]hexyl ester trifluoroacetate

**[0142]** To a solution of 0.108g of the intermediate prepared in Example 33 step A in 5mL of $CH_2Cl_2$ was added 20mg of 6-amino-hexanol, 28mg of HOBT, and 42mg of EDC and stirred for 4h. the reaction mixture was diluted with 10mL of $CH_2Cl_2$ and washed with 0.5N HCl (5mL), satureated aqueous $NaHCO_3$ (5mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (10g silica gel) with $CH_2Cl_2$-acetone (1:1) as eluent.

**[0143]** To 56.2mg of the above intermediate in 2mL of $CH_2Cl_2$ and 2mL of DMF was added 23mg of biotin, 14mg of DMAP, 28mg of EDC and stirred for 18h. The reaction was worked up in the ususal manner. Purification of the residue by flash chromatography over 5g of silica gel with $CH_2Cl_2$-acetone (1:1) as the eluent gave 22mg of the biotin conjugate. Deprotection of the N-tBOC was carried out in $CH_2Cl_2$-TFA to give 18.9mg of the title compound as a white solid. $^1H$ NMR ($CDCl_3$, 400MHz) The compound is a 3:2 mixture of rotamers. d 8.45-8.23 (m, 1H), 7.9 (s, 1H), 7.40-7.28 (m, 4H), 7.25-7.17 (m, 2H), 7.00 (dt, 2/3H), 6.80 (d, 1/3H), 5.21-5.14 (m, 1H), 4.60-4.42 (m, 4H), 4.28 (bt, 1H), 4.15-4.00 (m, 6H), 3.85-3.70 (m, 2H), 3.20-3.10 (m, 3H), 2.90 (dd, 1H), 2.83 (dt, 1H), 2.70 (d, 1H), 2.40-2.25 (m, 2H), 2.00-0.60 (m, 18H), 1.62 (s, 3H), 1.60 (s, 3H).

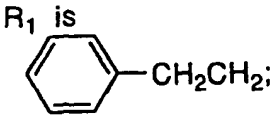
## Claims

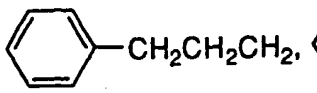
1. A compound of the formula:

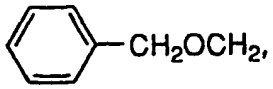


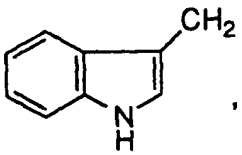
V

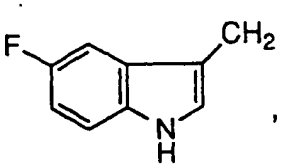
$R_1$ is

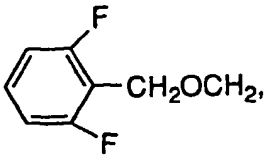


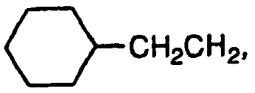


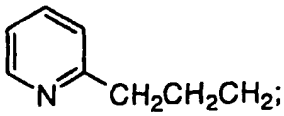


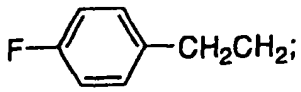


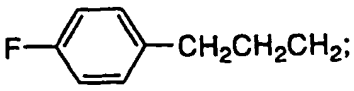






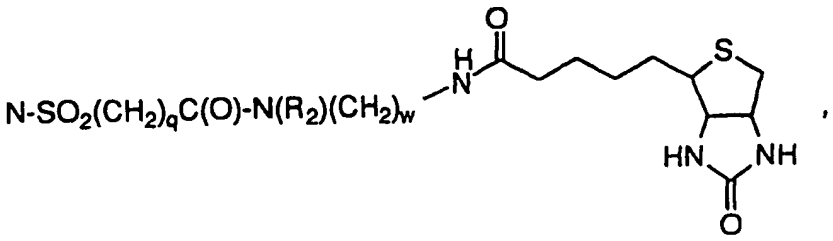


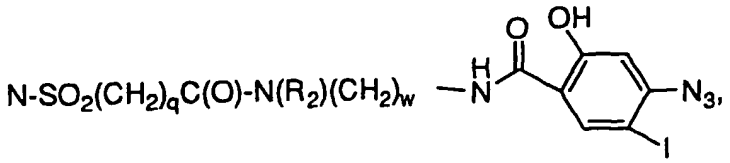


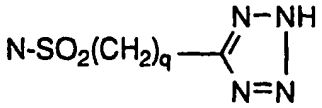


$R_{3a}$ is H, fluoro;

D is O, S, $S(O)_m$, $N(R_2)$, $NSO_2(R_2)$, $NSO_2(CH_2)_t$aryl, $NC(O)(R_2)$, $NSO_2(CH_2)_qOH$, $NSO_2(CH_2)_qCOOR_2$, $N\text{-}SO_2(CH_2)_qC(O)\text{-}N(R_2)(R_2)$, $N\text{-}SO_2(CH_2)_qC(O)\text{-}N(R_2)(CH_2)_wOH$,







and the aryl is phenyl or pyridyl and the phenyl may be substituted by 1-2 halogen;
$R_2$ is H, $C_1$-$C_4$ alkyl;
m = 1, 2;
t is 0, 1, 2;
q is 1, 2, 3;
w is 2-6;
and the pharmaceutically acceptable salts and individual diastereomers thereof.

2. A compound of Claim 1 which is:

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl) ethyl]-2-amino-2-methylpropanamide;

N-[1(R)-[(1,2-Dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl) ethyl]-2-amino-2-methylpropanamide;

N-[1(R)-[(1,2-Dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl) ethyl]-2-amino-2-methylpropanamide;

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethyloxy) ethyl]-2-amino-2-methylpropanamide;

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethyloxy) ethyl]-2-amino-2-methylpropanamide mesylate salt

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

N-1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-3-phenylpropyl]-2-amino-2-methylpropanamide;

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methylpropanamide; or

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-4-phenylbutyl]-2-amino-2-methylpropanamide;

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl)-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide

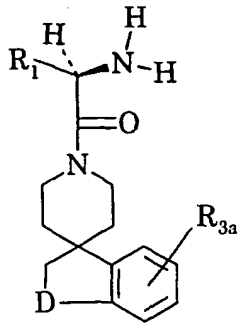
N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide

N-[1(R)-[(1,2-Dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3 -yl)ethyl]-2-amino-2-methylpropanamide

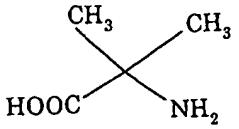
N-[1(R)-[(1,2-Dihydro-1,1dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy) ethyl]-2-amino-2-methylpropanamide

and pharmaceutically acceptable salts thereof.

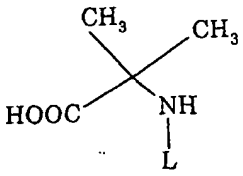
3. A process for the preparation of a compound of Claim 1 which comprises reacting a compound having a formula:



with a compound having the formula

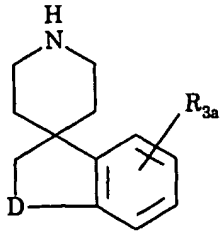


or

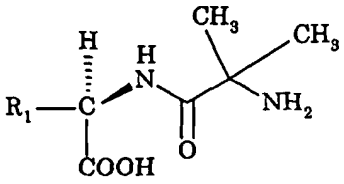


where $R_1$, $R_{3a}$ and D
are as defined in Claim 1 and L is a protecting group which is subsequently removed if present and salts are formed if desired.

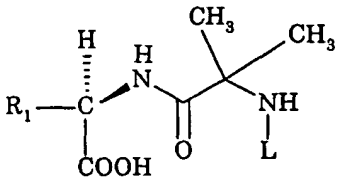
4. A process for the preparation of a compound of Claim 1 which comprises reacting a compound having a formula:



with a compound having the formula



or



where $R_1$, $R_{3a}$ and D
are as defined in Claim 1 and L is a protecting group which is subsequently removed if present and salts are formed if desired.

5. The use of a compound of Claim 1 for the manufacture of a medicament for increasing levels of endogenous growth hormone in a human or an animal.

6. A composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of a compound of Claim 1.

7. A composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of a compound of Claim I used in combination with other growth hormone secretagogues such as GHRP-6, GHRP-1, GHRP-2, growth hormone releasing factor (GRF), one of its analogs or IGF-1 or IGF-2.

8. The use of a bisphosphonate compound in combination with a compound of Claim 1 for the manufacture of a medicament for the treatment of osteoporosis.

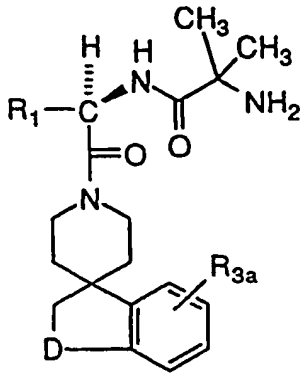
9. The use as claimed in Claim 8 wherein the bisphosphonate compound is alendronate.

10. A composition for the treatment of osteoporosis which comprises an inert carrier, a bisphosphonate compound and a compound of Claim 1.

11. The composition of Claim 10 where the bisphosphonate compound is alendronate.

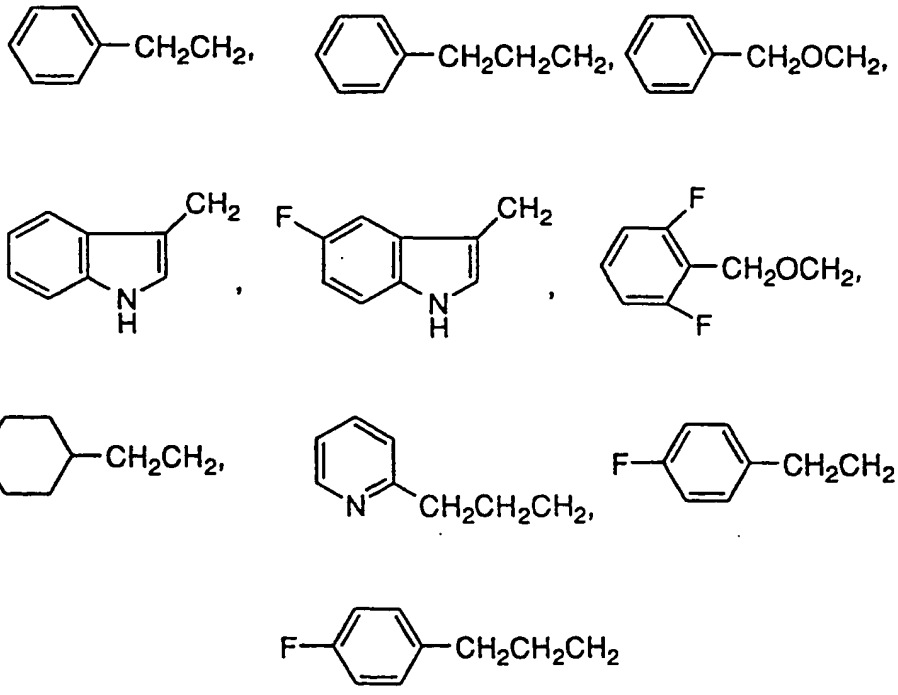
**Patentansprüche**

1. Eine Verbindung der Formel:

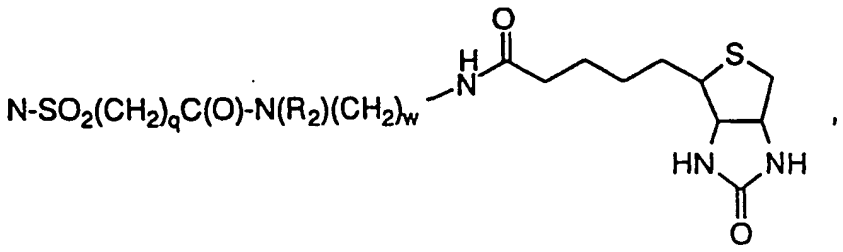


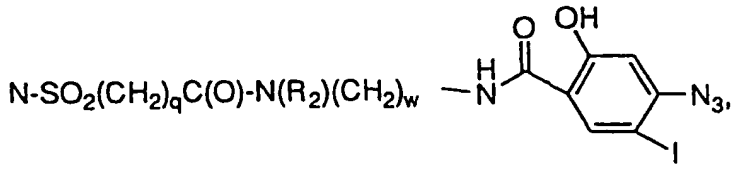
V

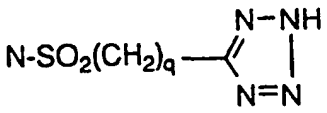
wobei
$R_1$



ist,
$R_{3a}$ H, Fluor ist,
D O, S, $S(O)_m$, $N(R_2)$, $NSO_2(R_2)$, $NSO_2(CH_2)_t$Aryl, $NC(O)(R_2)$, $NSO_2(CH_2)_qOH$, $NSO_2(CH_2)_qCOOR_2$, $N\text{-}SO_2(CH_2)_qC(O)\text{-}N(R_2)(R_2)$, $N\text{-}SO_2(CH_2)_qC(O)\text{-}N(R_2)(CH_2)_wOH$,







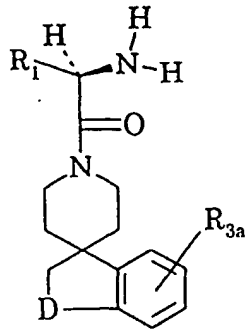
ist und das Aryl Phenyl oder Pyridyl ist und das Phenyl durch 1-2 Halogene substituiert sein kann,
$R_2$ H, $C_1$-$C_4$-Alkyl ist,
m = 1, 2,
t 0, 1, 2 ist,
q 1, 2, 3 ist,
w 2-6 ist,
und die pharmazeutisch annehmbaren Salze und einzelnen Diastereomere davon.

2. Eine Verbindung nach Anspruch 1, die ist:

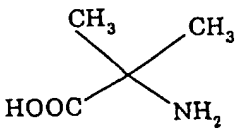
N-[1(R)-[(1,2-Dihydro-1-methansulfonylspiro[3H-indol-3,4'-piperidin]-1'yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamid,
N-[1(R)-[(1,2-Dihydro-1-methancarbonylspiro[3H-indol-3,4'-piperidin]-1'yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamid,
N-[1(R)-[(1,2-Dihydro-1-benzolsulfonylspiro[3H-indol-3,4'-piperidin]-1'yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamid,
N-[1(R)-[(1,2-Dihydro-1-methansulfonylspiro[3H-indol-3,4'-piperidin]-1'yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamid,
N-[1(R)-[(1,2-Dihydro-1-methansulfonylspiro[3H-indol-3,4'-piperidin]-1'yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamid-Mesylatsalz,
N-[1(R)-[(1,2-Dihydro-1-methansulfonylspiro[3H-indol-3,4'-piperidin]-1'yl)carbonyl]-2-(2',6'-difluorphenylmethyloxy)ethyl]-2-amino-2-methylpropanamid,
N-[1(R)-[(1,2-Dihydro-1-methansulfonyl-5-fluorspiro[3H-indol-3,4'piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamid,
N-1(R)-[(1,2-Dihydro-1-methansulfonylspiro[3H-indol-3,4'-piperidin]-1'yl)carbonyl]-3-phenylpropyl]-2-amino-2-methylpropanamid,
N-[1(R)-[(1,2-Dihydro-1-methansulfonylspiro[3H-indol-3,4'-piperidin]-1'yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methylpropanamid oder
N-[1(R)-[(1,2-Dihydro-1-methansulfonylspiro[3H-indol-3,4'-piperidin]-1'yl)carbonyl]-4-phenylbutyl]-2-amino-2-methylpropanamid,
N-[1(R)-[(1,2-Dihydro-1-methansulfonylspiro[3H-indol-3,4'-piperidin]-1'yl)carbonyl]-2-(5-fluor-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamid,

N-[1(R)-[(1,2-Dihydro-1-methansulfonyl-5-fluorspiro[3H-indol-3,4'piperidin]-1'-yl)carbonyl]-2-(5-fluor-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamid,
N-[1(R)-[(1,2-Dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indol-3,4'-piperidin)-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamid,
N-[1(R)-[(1,2-Dihydro-1,1-dioxospiro[3H-benzothiophen-3,4'-piperidin]-1'yl)carbonyl]-2-(phenylmethyloxy) ethyl]-2-amino-2-methylpropanamid, und pharmazeutisch annehmbare Salze davon.

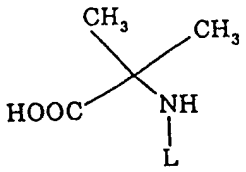
3. Ein Verfahren zur Herstellung einer Verbindung nach Anspruch 1, das die Umsetzung einer Verbindung mit einer Formel:



mit einer Verbindung mit der Formel

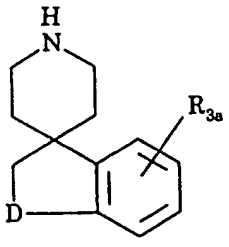


oder

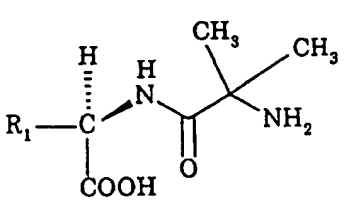


umfaßt, wobei $R_1$, $R_{3a}$ und D
wie in Anspruch 1 definiert sind und L eine Schutzgruppe ist, die, falls sie vorhanden ist, anschließend entfernt wird und wobei, falls erwünscht, Salze gebildet werden.

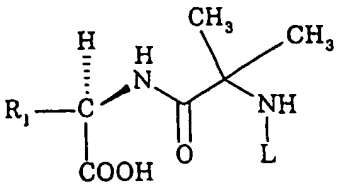
4. Ein Verfahren zur Herstellung einer Verbindung nach Anspruch 1, das die Umsetzung einer Verbindung mit einer Formel:



mit einer Verbindung mit der Formel



oder



umfaßt, wobei $R_1$, $R_{3a}$ und D
wie in Anspruch 1 definiert sind und L eine Schutzgruppe ist, die, falls sie vorhanden ist, anschließend entfernt wird und wobei, falls erwünscht, Salze gebildet werden.

5. Die Verwendung einer Verbindung nach Anspruch 1 zur Herstellung eines Medikaments zur Erhöhung des Spiegels an endogenem Wachstumshormon in einem Menschen oder einem Tier.

6. Eine zur Erhöhung der endogenen Produktion oder Freisetzung von Wachstumshormon in einem Menschen oder einem Tier geeignete Zusammensetzung, die einen inerten Träger und eine wirksame Menge einer Verbindung nach Anspruch 1 enthält.

7. Eine zur Erhöhung der endogenen Produktion oder Freisetzung von Wachstumshormon in einem Menschen oder einem Tier geeignete Zusammensetzung, die einen inerten Träger und eine wirksame Menge einer Verbindung nach Anspruch 1 enthält, die in Kombination mit anderen die Sekretion von Wachstumshormon anregenden Mitteln, wie z.B. GHRP-6, GHRP-1, GHRP-2, Wachstumshormonreleasingfaktor (GRF), eines seiner Analoga oder IGF-1 oder IGF-2, verwendet wird.

8. Die Verwendung einer Bisphosphonatverbindung in Kombination mit einer Verbindung nach Anspruch 1 zur Herstellung eines Medikaments zur Behandlung von Osteoporose.

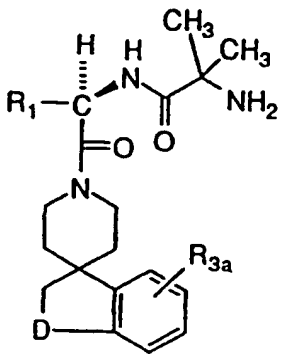
9. Die wie in Anspruch 8 beanspruchte Verwendung, wobei die Bisphosphonatverbindung Alendronat ist.

10. Eine Zusammensetzung zur Behandlung von Osteoporose, die einen inerten Träger, eine Bisphosphonatverbindung und eine Verbindung nach Anspruch 1 enthält.

11. Die Zusammensetzung nach Anspruch 10, wobei die Bisphosphonatverbindung Alendronat ist.

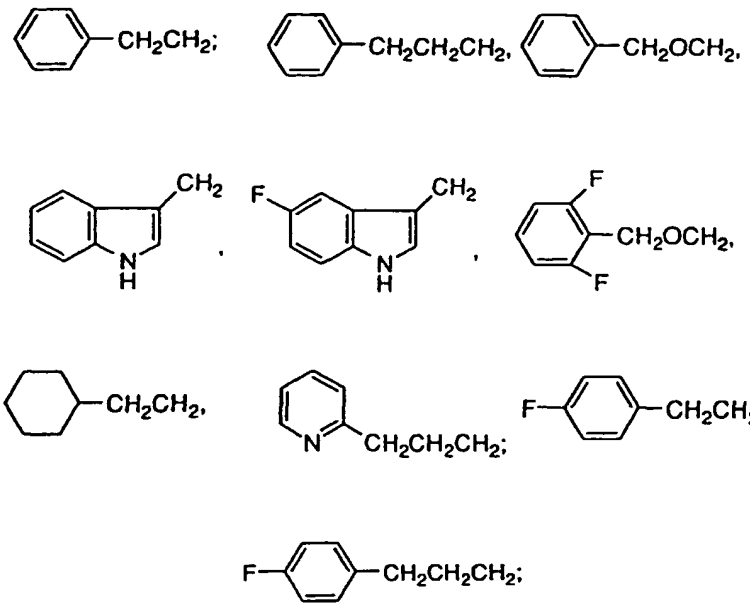
**Revendications**

1. Composé ayant la formule suivante :

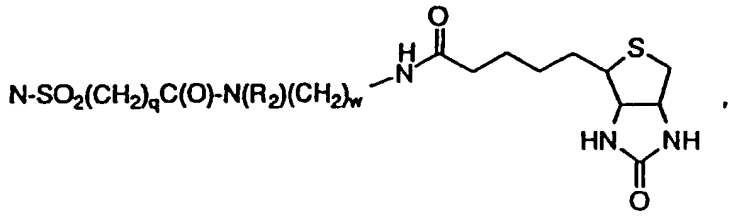


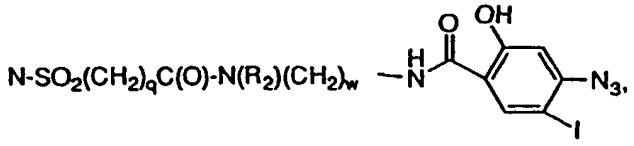
V

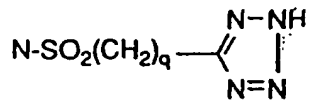
$R_1$ est



$R_{3a}$ est H, un groupe fluoro,
D est O, S, $S(O)_m$, $N(R_2)$, $NSO_2(R_2)$, $NSO_2(CH_2)_t$aryle, $NC(O)(R_2)$, $NSO_2(CH_2)_qOH$, $NSO_2(CH_2)_qCOOR_2$, $N\text{-}SO_2(CH_2)_qC(O)\text{-}N(R_2)(R_2)$, $N\text{-}SO_2(CH_2)_qC(O)\text{-}N(R_2)(CH_2)_wOH$,







et l'aryle est un phényle ou un pyridyle et le phényle peut être substitué par un composé 1-2 halogène,
$R_2$ est H, un alkyle $C_1$-$C_4$,

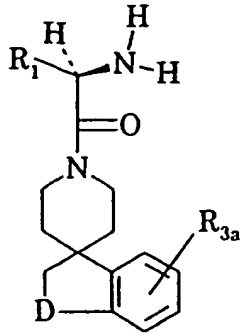
m = 1, 2,
t est égal à 0, 1, 2,
q est égal à 1, 2, 3,
w est compris entre 2 et 6,
et les sels pharmaceutiquement acceptables et diastéréo-isomères individuels de ceux-ci.

2. Composé selon la revendication 1, qui est :

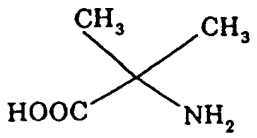
N-[1(R)-[(1,2-Dihydro-1-méthanesulfonylspiro[3H-indole-3,4'-pipéridine]-1'-yle)carbonyle]-2-(lH-indole-3-yle) éthyle]-2-amino-2-méthylpropanamide,
N-[1(R)-[(1,2-Dihydro-1-méthanecarbonylspiro[3H-indole-3,4'-pipéridine]-1'-yle)carbonyle]-2-(1H-indole-3-yle)éthyle]-2-amino-2-méthylpropanamide,
N-[1(R)-[(1,2-Dihydro-1-benzènesulfonylspiro[3H-indole-3,4'-pipéridine]-1'-yle)carbonyle]-2-(1H-indole-3-yle)éthyle]-2-amino-2-méthylpropanamide,
N-[1(R)-[(1,2-Dihydro-1-méthanesulfonylspiro[3H-indole-3,4'-pipéridine]-1'-yle)carbonyle]-2-(phénylméthyloxy) éthyle]-2-amino-2-méthylpropanamide,
sel de N-[1(R)-[(1,2-Dihydro-1-méthanesulfonylspiro [3H-indole-3,4'-pipéridine]-1'-yle)carbonyle]-2-(phénylméthyloxy)éthyle]-2-amino-2-méthylpropanamide mésylate
N-[1(R)-[(1,2-Dihydro-1-méthanesulfonylspiro[3H-indole-3,4'-pipéridine]-1'-yle)carbonyle]-2-(2',6'-difluorophénylméthyloxy)éthyle]-2-amino-2-méthylpropanamide,
N-[1(R)-[(1,2-Dihydro-1-méthanesulfonyle-5-fluorospiro [3H-indole-3,4'-pipéridine]-1'-yle)carbonyle]-2-(phényl méthyloxy)éthyle]-2-amino-2-méthyl-propanamide,
N-[1(R)-[(1,2-Dihydro-1-méthanesulfonylspiro[3H-indole-3,4'-pipéridine]-1'-yle)carbonyle]-3-phénylpropyle]-2-amino-2-méthylpropanamide,
N-[1(R)-[(1,2-Dihydro-1-méthanesulfonylspiro[3H-indole-3,4'-pipéridine]-1'-yle)carbonyle]-3-cyclohexylpropyle]-2-amino-2-méthylpropanamide, ou
N-[1(R)-[(1,2-Dihydro-1-méthanesulfonylspiro[3H-indole-3,4'-pipéridine]-1'-yle)carbonyle]-4-phénylbutyle]-2-amino-2-méthylpropanamide,
N-[1(R)-[(1,2-Dihydro-1-méthanesulfonylspiro[3H-indole-3,4'-pipéridine]-1'-yle)carbonyle]-2-(5-fluoro-1H-indole-3-yle)éthyle]-2-amino-2-méthylpropanamide
N-[1(R)-[(1,2-Dihydro-1-méthanesulfonyle-5-fluorospiro[3H-indole-3,4'-pipéridine]-1'-yle)carbonyle]-2-(5-fluoro-1H-indole-3-yle)éthyle]-2-amino-2-méthylpropanamide
N-[1(R)-[(1,2-Dihydro-1-(2-éthoxycarbonyle)méthylsulfonyl spiro-[3H-indole-3,4'-pipéridine]-1'-yle)carbonyle]-2-(1H-indole-3-yle)éthyle]-2-amino-2-méthylpropanamide
N-[1(R)-[(1,2-Dihydro-1,1dioxospiro-[3H-benzothiophène-3,4'-pipéridine]-1'-yle)carbonyle]-2-(phénylméthyloxy) éthyle]-2-amino-2-méthylpropanamide

et des sels pharmaceutiquement acceptables de ceux-ci.

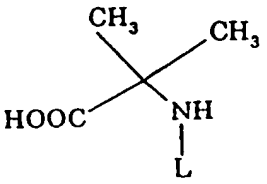
3. Procédé pour la préparation d'un composé selon la revendication 1, qui comporte la réaction d'un composé ayant la formule suivante :




avec un composé ayant la formule suivante

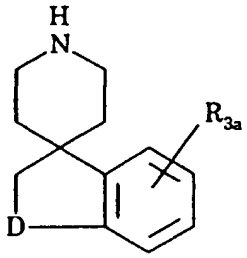


ou

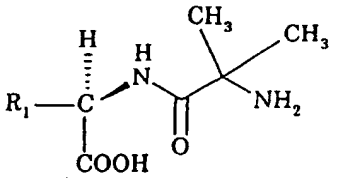


où $R_1$, $R_{3a}$ et D sont tels que définis dans la revendication 1 et L est un groupe protecteur qui est par la suite éliminé s'il est présent et des sels sont formés si on le souhaite.

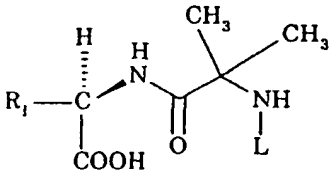
4. Procédé pour la préparation d'un composé selon la revendication 1, qui comporte la réaction d'un composé ayant la formule suivante :



avec un composé ayant la formule suivante



ou



où $R_1$, $R_{3a}$ et D sont tels que définis dans la revendication 1 et L est un groupe protecteur qui est par la suite éliminé s'il est présent et des sels sont formés si on le souhaite.

5. Utilisation d'un composé selon la revendication 1 pour la fabrication d'un médicament destiné à augmenter des niveaux d'hormone de croissance endogène chez un humain ou un animal.

6. Composition utile pour augmenter la production ou la libération endogène d'hormone de croissance chez un humain ou un animal qui comporte un support inerte et une quantité efficace d'un composé selon la revendication 1.

7. Composition utile pour augmenter la production ou la libération endogène d'hormone de croissance chez un humain ou un animal qui comporte un support inerte et une quantité efficace d'un composé selon la revendication 1, utilisée en combinaison avec d'autres sécrétagogues d'hormone de croissance tels que GHRP-6, GHRP-1, GHRP-2, le facteur de libération d'hormone de croissance (GRF), un de ses analogues ou IGF-1 ou IGF-2.

8. Utilisation d'un composé de bisphosphonate en combinaison avec un composé selon la revendication 1, pour la fabrication d'un médicament pour le traitement de l'ostéoporose.

9. Utilisation selon la revendication 8, dans laquelle le composé de bisphosphonate est un alendronate.

10. Composition pour le traitement de l'ostéoporose qui comporte un support inerte, un composé de bisphosphonate

et un composé selon la revendication 1.

11. Composition selon la revendication 10, où le composé de bisphosphonate est un alendronate.